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Editorial

Hypertension and Arteriosclerosis

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"Hypertensive-arteriosclerotic cardiovascular disease" represents terminology widely used in medicine. Although vague, diffuse, nonspecific, and generally unacceptable in modern cardiovascular diagnosis, such terminology, in its genesis and propagation, represents interpretations of observations made by physicians over many years. This term arose from frequent clinical-pathologic associations of two different cardiovascular diseases, namely, hypertension and arteriosclerosis (atherosclerosis). The direction in which the association was first approached is unclear. Regardless of the obvious errors in terminology, the reflected association is important. It emphasizes the potent causative factor of hypertension in the pathogenesis of atherosclerosis. It appears worth while to re-emphasize this relationship of hypertension to atherosclerosis from time to time, lest it be lost in the rapidly growing maze of humoral and lipid metabolic data.

Terminology in the literature relating to "arteriosclerosis" is still confusing. Although cognizant of differing views held by investigators, we shall proceed with the following definitions. *Atheromatosis* or *atherosis* is viewed as endothelial proliferation in plaques, with lipid deposits primarily in the intima of the large and medium arteries. *Arteriosclerosis* is conveniently a less binding term and may be viewed as a lesion capable of involving the whole arterial tree, characterized by hypertrophic changes and an increase in fibrous elements of the arterial walls. Although either process may occur separately, a combination is common and is best termed *atherosclerosis*, although by general usage, *arteriosclerosis* applies here also.

In many of the examples to follow it might be argued that the lesions are not related to true atherogenesis, and the importance of defects in general lipid

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metabolism and localized lipid deposits is neglected. Such is not the case. Harmony between views on "sclerotic" vascular lesions with and without lipid deposits may be developed. It is known that hypercholesterolemia is not essential for the production of atherosclerosis. Over the appropriate time, with increased intra-arterial pressure and even a normal content of lipids in the blood, such lesions develop.[1,2]

Many observations can be offered to support the contention that hypertension is one of the potent and already established factors in the pathogenesis of atherosclerosis. For example, the infrequency of significant arteriosclerotic vascular lesions in the low-pressure pulmonary arterial circuit and the entire venous system of man is well known and is remarkable in contrast to the arteriosclerotic lesions found in the systemic arterial circulation. This is so, even though blood with essentially the same constitution of lipids flows through all blood vessels. However, if by some means the pressure in the lesser circulation increases, arteriosclerotic lesions develop. Such changes have been noted in the pulmonary arteries in association with diseases that produce pulmonary hypertension, such as large patent ductus arteriosus, primary pulmonary hypertension, and pulmonary embolism.[3-5] Pulmonary arteriosclerosis follows procedures such as the Potts and Blalock-Taussig operations in cases of tetralogy of Fallot, and these changes have also occurred in experimentally produced aortic-pulmonary arterial communications in animals.[4] It is of interest that atherosclerosis may form even in the pulmonary arteries of young children following the Potts or Blalock-Taussig operations with openings of critical size. In such cases, of course, there is no atheromatosis in the aorta, and abnormalities of serum lipids are not apparent. The important factor is that the existing pressures are "normal" for the aortic structure but hypertensive for the pulmonary arterial system. One wonders how the process of atherosclerosis would progress in the aorta over a lifetime if it were possible to maintain a systemic arterial blood pressure at very low levels, such as in the pulmonary arteries.

Interesting experiments occurring in nature have been observed with respect to the systemic circulation itself. In coarctation of the aorta, severe atherosclerosis is found in the areas of highest tension, namely, proximal to the obstruction, whereas the vessels distal to the immediate area of the obstruction may be relatively free of pathologic change. A similar situation has been noted in areas proximal and distal to complete occlusion of the aortic bifurcation in the Leriche syndrome.[6] After surgical correction of this situation, atherosclerosis is noted to progress in these distal areas which were previously much less involved. This progression is noted to occur in older individuals at a much faster rate than in younger individuals with similar pressures and concentrations of lipids. These observations suggest the presence of an additional "tissue factor" in the pathogenesis of the lesions.

That the kinetic effects of blood flow may be important in atherogenesis is suggested from further observations. In the human thoracic aorta, atherosclerotic lesions are found to be more predominant on the outer circumference of the distal arch and the fixed posterior wall[1]: those portions are subjected to the greatest kinetic energy from the flowing blood. The increased frequency of

atherosclerotic lesions at sites of bifurcation is well known.[7] Experimentally in dogs, if the aorta is united with the left main pulmonary artery, the resulting vascular changes in the pulmonary circuit are several times more severe on the left than on the right, even though the increased pressure is reflected to both sides of the pulmonary arterial system.[4] Again, this is probably related to the kinetics of blood flow.

Studies in experimental atherosclerosis have offered additional clues. If cholesterol-fed rabbits are treated with phenobarbital, the cholesterol content of the blood changes little, but the arterial systolic and diastolic blood pressures are regularly decreased. In comparison with the findings in control groups of cholesterol-fed rabbits, the development of atherosclerotic changes in the aorta is quite markedly reduced.[8] The accentuating effects of hypertension on the severity of atheromatosis in the experimental animal is well established in other studies.[9,10]

The importance of hypertension in producing atherosclerotic lesions is suggested from still other observations. The great preponderance of such lesions in the lower extremities of man, as compared with those in the upper extremities, is well known. Arteriosclerotic obliterative disease with gangrene is rare in the hands and relatively common in the feet. Again, this is conceivably related to the forces of greater pressure acting on the vessels of the lower extremities, under the addition of gravitational influences. Interesting similar gravitational factors dependent on body build have been postulated to explain variation in occurrence and distribution of atheromatous lesions in cerebral and other arteries.[11]

The low-pressure system of veins is regularly free of sclerotic lesions. After fatty meals the lacteals and mesenteric veins contain the highest recorded levels of fat and cholesterol, but atherosclerosis does not develop in these vessels. In cases of long-standing venous hypertension, however, sclerotic lesions are observed. Thus, in cases of varicosities and arteriovenous fistulae of long duration, significant phlebosclerosis may be found.[1,7] Sclerosis of the veins of the portal system has been found to be very common in patients with hypertension in this circuit arising from portal cirrhosis and chronic obstructions of the portal vein.[1] Furthermore, phlebosclerosis of the hepatic veins has been commonly found in patients with prolonged periods of high venous pressures.[1] Whether these lesions are pathogenetically related to atherogenesis is debatable, but the analogy exists.

The much greater incidence and severity of atherosclerosis in males than in females is generally well accepted. If, however, females with diastolic hypertension are studied, this difference is not so easily demonstrated.[12,13] It is generally accepted that people with hypertension show a quite significantly increased frequency and severity of atherosclerosis in the coronary arteries,[12-14] the renal arteries,[15] and the cerebral arteries.[16] Moreover, it has been shown that patients with essential hypertension have a significantly increased content of cholesterol and fat in their aortas for a given age as compared with that in the general population, and this has held true even in the presence of normal concentrations of serum cholesterol.[2,17] Analysis of statistics has suggested that people with blood pressures below "normal" have more favorable mortality rates.[18]

Just how hypertension brings about these changes is not clear. In all examples cited above, the degree and duration of hypertension is important. The hypertensive factor may be related to structural damage of the vascular wall, to interruption of the blood supply through the vasa vasorum, to augmentation of lipid deposition, to "wear and tear," or to many other possibilities. Regardless of the cause, however, the relationship between hypertension and atherosclerosis appears to be clear-cut and constant.

It should again be recalled that blood which has essentially the same content of lipids flows through all of the vessels of the body. Atherosclerosis, however, is regionally different in extent, and thus certain localizing and propagating factors are important. This idea, of course, is far from being new, but it tends to be lost sight of in the current feverish investigations into lipid metabolic defects.

It is important, furthermore, to realize that one cannot deal exclusively with diffuse terms such as "generalized arteriosclerosis." The location of the lesions appears to be of paramount importance. For example, it is not possible to equate reliably coronary atherosclerosis with cerebral or peripheral vascular arteriosclerosis. Wide individual and racial variations here are established and well known.[19]

It is not suggested that hypertension is the most important localizing factor for atherogenesis in all segments of the circulation. The coronary arterial system may present a completely different situation from that which exists in the aorta and other large vessels. For example, the potentiating and propagating effects of epinephrine and norepinephrine in atherogenesis appear to be well established.[20-22] One wonders then about the significance of the collection of chromaffin tissue along the left coronary sulcus. This is one of the few extra-adrenal locations of chromaffin tissue known to exist in the body.[23]

From a general and broad viewpoint, however, with all things being equal and with respect to any given segment of the circulation, it appears that it would be much more preferable to have elevated concentrations of cholesterol rather than elevated blood pressure if one wished to reduce the rate and extent of atherosclerosis. For any given level of arterial pressure it is possible that alterations in lipid metabolism are related to atherogenesis. However, regardless of the abundant data on lipid metabolism which are being accumulated to explain the etiology of atherogenesis, the importance of the localizing causative factors appears paramount. Of these factors, hypertension is reliable and established for man.

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Clinical Communications

The Vascularized Cardiac Thrombus as a Possible Vicarious Source of Blood Supply in Ischemic Human Hearts

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A thrombus in the heart undergoes much the same evolutionary change as elsewhere. It is covered by endothelium, and organized by fibroblasts and capillaries. In time, a more or less vascular connective tissue replaces part or all of the clot.

In large vessels, the invasion of the thrombus by capillaries proceeds from the wall of the vessel involved, and from the patent parts of the lumen. New capillaries which originate from one of these sources may connect with those derived from the other.[1,2] Through communications thus established, blood from the lumen of the vessel may enter the vasa vasorum.

It appeared possible that new vascular channels formed in the cardiac thrombus may similarly convey blood from the lumen of the heart to the myocardium. Our aim was to test this hypothesis anatomically.

The study reported upon here was confined to thrombi associated with infarcts in the left ventricle of human hearts, and deals with the presence or absence of vascular intercommunications between the lumen of the left ventricle, the thrombus, and the myocardium. We have been unable to find reference to similar studies on record. A detailed account of the vascularization of thrombi in various chambers of hearts with and without infarcts will be given in a subsequent report.

MATERIALS AND METHODS

The hearts on which this study is based were processed in three ways.

Group A: One Hundred Hearts Studied by Routine Autopsy Methods.—Histologic sections from hearts with thrombi and infarcts in the left ventricle, obtained from a consecutive series of

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autopsies, were reviewed. Those from 100 of these hearts were selected because: (a) the thrombus was richly vascularized, and (b) the attachment of the thrombus to the wall of the heart could be demonstrated in the available section. The sections were stained with hematoxylin-eosin or phloxine-methylene blue. Supplementary sections prepared with Verhoeff's elastic tissue stain were available from a number of specimens.

Group B: Eight Hearts Studied by a Modification of Schlesinger's Coronary Injection Method.[3]—Eight hearts with old thrombi and healed infarcts in the left ventricle were picked from a series studied by a modification of Schlesinger's coronary injection method. The coronary arteries were injected with a radiopaque mass,[4] laid out in one plane,[5] visualized roentgenographically, and dissected. The mass consists of barium sulfate in a menstruum of gelatin. It penetrates regularly to arterioles which are 40 to 50 micra in diameter, inconstantly to smaller arterioles, and does not enter capillaries. A pneumatic apparatus in which the pressure may be accurately controlled was used for injection. The injection pressure was gradually raised to 200 mg. Hg, and was maintained at that level for 5 minutes; then the injection was ended. The ventricles were coronally sliced at intervals of 0.5 cm. Stereoscopic angiograms of the slices were prepared (100 Ma., 42 kv., 0.75 second, 40 inches from tube to film). Histologic sections were stained with hematoxylin-eosin, Masson's trichrome, and Verhoeff's elastic tissue.

Group C: Four Hearts Studied by a Modification of Schlesinger's Coronary Injection Method Combined With the Injection of India Ink Into the Left Ventricle.—A series of hearts were studied by a modification of Schlesinger's method (as in Group B) combined with the injection of India ink into the left ventricle. Four of these hearts had infarcts and thrombi in the left ventricle. A healed infarct and an old thrombus were present in one; a healed infarct and old and recent thrombi were present in a second; a recent infarct and a recent thrombus were found in a third; and a fourth had recent and healed infarcts associated with old and recent thrombi. All these thrombi were vascularized.

India ink (Higgins) diluted with water (1 part to 3 parts) was injected into the left ventricle after the coronary arteries had been injected with Schlesinger's barium sulfate–gelatin mass. The intraventricular injection was accomplished through large cannulae (syringes with plungers removed served the purpose) secured into the openings of the mitral and aortic valves and connected to the pneumatic apparatus. At the aortic valvular opening, the cannula was secured below the coronary ostia. The ink was injected under controlled pressure. The pressure was gradually raised to 200 mm. Hg, and maintained at that level for 10 to 15 minutes, after which the injection was terminated. The heart was then examined as in Group B.

OBSERVATIONS

Group A.—Histologic sections of the hearts in Group A included some showing superficial vessels of the thrombus which opened into the cardiac lumen, and other vessels deeper down which entered the myocardium.

Communications between vessels of the thrombus and the cardiac lumen: An occasional endothelialized channel leading from the free surface of the thrombus into its substance could be demonstrated in the histologic sections of 31 of the 100 hearts surveyed. These channels were slightly larger than the other vessels of the thrombus into which they led, and usually had funnel-shaped entrances with the wide end presenting toward the cardiac lumen (Fig. 1.). Their openings were found in the vicinity of the endocardial attachments of the thrombus, often on aspects facing the depths of the intertrabecular spaces.

Communications between vessels of the thrombus and the coronary system: Communications between vessels of the thrombus and those of the myocardium were demonstrated in the histologic sections from 42 hearts. In 9 of the specimens, communications with the cardiac lumen were also observed.

The vascular connections or bridges between the vessels of the thrombus and those of the myocardium were few and widely spaced, were the size of capillaries

(Fig. 2) or larger (Fig. 3), and crossed areas of the endocardium which had defects in the layer of elastic fibers (Fig. 3). The connections were with dilated vessels of surviving myocardium overlying recent, healing, or healed infarcts; or with vessels of the granulation tissue or the scar tissue in areas in which the infarction did not spare the subendocardial zone.

The demarcation of the thrombus from the myocardium generally could be easily made out despite the presence of vascular communications between them. The exceptions were 6 specimens in which parts of the organizing tissue of the thrombus blended imperceptibly into the granulation tissue of healing infarcts directly adjacent to the thrombus. In these areas, the endocardium itself seemed to be replaced by granulation tissue, and it was impossible to determine whether this had originated from the thrombus or the myocardium.

Groups B and C.—Study of the hearts in Group A gave no proof of any continuity between vessels leading from the cardiac lumen into the thrombus, and those extending from the thrombus to the myocardium. Proof of this was obtained by the injection methods used in Groups B and C. It appears that intercommunications do exist between the cardiac lumen, the vessels of the thrombus, and the coronary system; and that such intercommunications may be missing or interrupted at various levels.

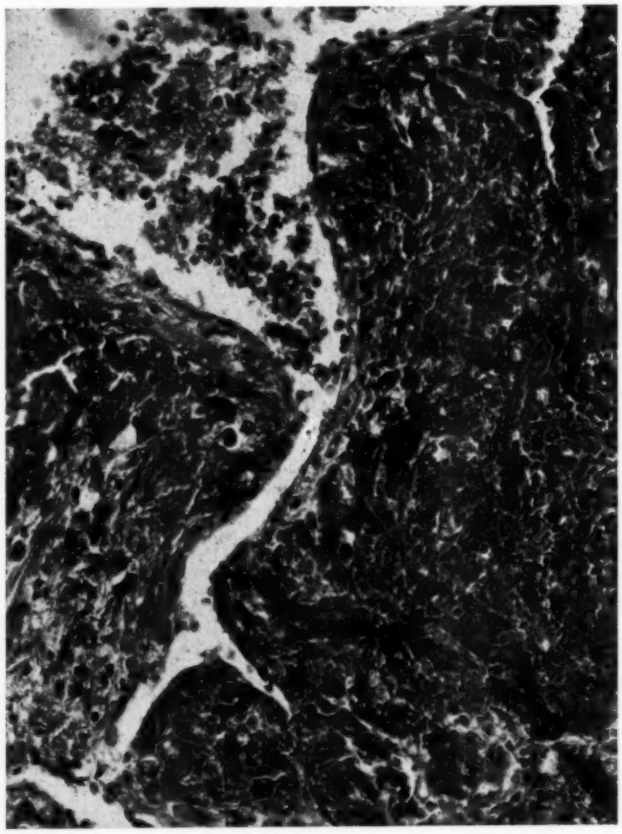

Fig. 1.—Part of organizing thrombus, showing endothelialized inlet on its surface leading into new vessels in its substance. (Phloxine-methylene blue, ×400; reduced ⅓.)

Complete vascular intercommunications between the cardiac lumen, the thrombus, and the coronary system: Complete intercommunications between the cardiac lumen, the vessels of the thrombus, and the coronary system were demonstrated in 9 of the 12 hearts comprising Groups B and C. The presence of such intercommunications was established in 2 specimens by the passage of India ink from the cardiac lumen, through the vessels of the thrombus, into the vessels of the myocardium; in 5, by the leakage of Schlesinger's barium sulfate–gelatin mass from the coronary arteries, through the vessels of the thrombus, into the cardiac lumen; and in 2 others, by the leakage of the mass into the cardiac lumen and the presence of both ink and mass intermixed inside vessels of the thrombus. The intercommunications appeared to be of smaller caliber in 2 hearts with organizing recent thrombi than in 7 with old ones.

Fig. 2.—Capillary bridge between base of organizing thrombus (*upper part of photograph*) and myocardium (*lower part*). (Hematoxylin-eosin, ×400; reduced ⅓.)

Vessels containing ink were found in organizing recent thrombi of 2 (Group C) hearts. Since the ink was introduced directly into the left ventricular cavity, access to these vessels must have been through communications with the cardiac lumen. Vascular openings on the free surface of the thrombus were noted, and vessels filled with ink were traced from the thrombus to the myocardium, indicating that the communications did extend into parts of the coronary system.

Schlesinger's barium sulfate–gelatin mass injected into the coronary arteries failed to enter the vessels of the thrombus in both specimens. Since India ink enters vessels as small as capillaries, whereas the mass penetrates not much farther than arterioles 40 micra in size, these findings indicate that the connecting channels between the coronary arteries and the vessels of the thrombus were narrower than 40 micra somewhere along their course through the ventricular wall.

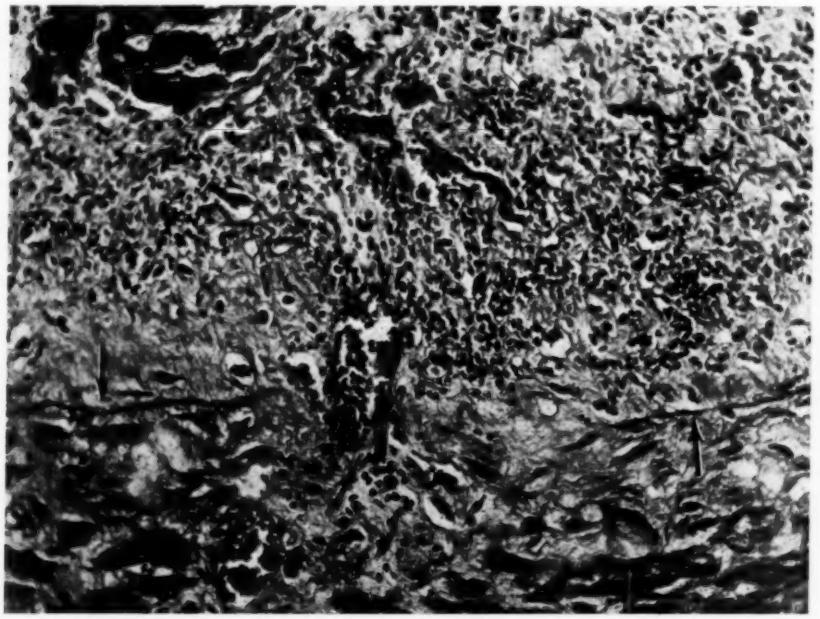

Fig. 3.—Junction of organizing thrombus and ventricular wall. Vascular bridge traversing patch of endocardium deficient in elastic fibers (*arrows*). (Verhoeff's elastic tissue, ×360; reduced ⅓.)

Schlesinger's mass leaked directly into the lumen of the left ventricle of 7 hearts with old thrombi (5 Group B, 2 Group C). The old thrombus in 2 of these hearts (1 Group B, 1 Group C) was fully replaced by dense fibrous tissue, and the process of organization appeared to have long run its course. The entrance of mass into the ventricular cavity could not be dismissed as a mechanical post-mortem artifact because the injected vessels were all lined by endothelium, and no extravasation of mass could be detected in the myocardium or the thrombus. The area of the cardiac wall where the leaks occurred was identifiable in the gross, and corresponded in all 7 hearts with the zone of healed infarction bearing the old thrombus. Vessels filled with mass were observed to pass from the myocardium to the thrombus, and to lead from the body of the thrombus to the cardiac lumen, in the stereoangiograms of 2 specimens (Fig. 4) and in the histologic sections of all 7 specimens (Figs. 5 and 6). The largest such vessel noted to cross the endocardium was 400 micra in diameter (Fig. 6). India ink injected into the left ventricle of 2 of these hearts was found in both instances to be intermixed with mass inside vessels of the thrombus (Fig. 7). The conclusion

drawn was that the entrance of the mass into the cardiac lumen occurred, at least in part,* through vessels of the old thrombus, and that in all 7 hearts, patent channels of substantial size (i.e., at least 40 micra in diameter) extended without interruption from the coronary arteries, through the vessels of the old thrombus, into the lumen of the left ventricle.

Lack of complete vascular intercommunications between the cardiac lumen, the thrombus, and the coronary system: Segments of the intercommunicating channels between the lumen of the left ventricle, the thrombus, and the coronary system appeared to be missing in 5 of the injected hearts (2 Group C, 3 Group B).

Fig. 4.—Angiogram of slice of left ventricular wall bearing old thrombus (*lines*). Arterialization of organized basal parts of thrombus (*long arrow*). Injected vessels connect with pools of radiopaque mass in intertrabecular extensions of cardiac lumen (*short arrows*). (Positive print, ×1.5; reduced ⅓.)

An actively organizing thrombus in one (Group C) heart had vessels filled only with ink, and did not show vascular bridges to the myocardium (Fig. 8). Evidently, the connecting channels which led from the cardiac lumen extended no farther than the confines of the thrombus. An old thrombus also present in this heart contained vessels filled with both ink and mass (Fig. 7).

An old thrombus in another (Group C) heart was completely organized, and only a few endothelialized spaces, none of which contained ink or mass, could be found in its substance. Neither vascular bridges to the myocardium nor openings to the cardiac lumen were detected, and the vascular elements of the thrombus thus appeared to be isolated from both the cardiac lumen and

*Leakage of Schlesinger's barium sulfate–gelatin mass from the coronary arteries into the lumen of the left ventricle was also observed in hearts with healed infarcts without endocardial thrombi. These cases will be described in a separate report.

the coronary system. An organizing recent thrombus which coexisted in the same specimen had ink-filled vessels crossing the endocardium into the myocardium.

Leakage of Schlesinger's mass into the lumen of the left ventricle did not occur in the remaining 3 (Group B) hearts with healed infarcts and old thrombi. The extent of mural thrombosis and of ischemic damage in these hearts differed in no obvious manner from that of the other hearts in which leakage was observed.

Fig. 5.—Old organized thrombus containing vessels filled with radiopaque mass (*long arrow*). Lower portion of photograph shows whole thickness of scarred ventricular wall; upper portion, which appears black, is body of old thrombus converted into dense fibrous tissue. Cross sections of columnae carneae in upper right corner. Radiopaque mass in depths of intertrabecular spaces (*short arrows*). (Masson's trichrome, ×12; reduced ¼.)

The coronary arteries concerned were patent up to the borders of the infarcted zone which bore the thrombus, the zone itself being devoid of injected vessels (Fig. 9). Although injection of India ink had not been made in these hearts, vascular openings on the free surface of the thrombus, and vascular bridges to the myocardium were demonstrated histologically. Arteries larger than 40 micra and uninjected with mass were present in the organized parts of the thrombus and in the subjacent ventricular wall. At the latter site there were islands of surviving myocardium amidst the scar. Evidently, in these 3 cases, passages extending from the main coronary arteries, through the old thrombus, into the cardiac lumen had become closed off within the wall of the ventricle itself.

DISCUSSION

The evidence presented seems to indicate that in infarcted human hearts with cardiac thrombi, (1) vascular communications may form between the lumen of the left ventricle, the vessels of the organizing thrombus, and the coronary system; (2) these communications may persist in old thrombi; and (3) those which persist can be of substantial size, and can extend as such into the coronary arterial tree. Investigations to define how these communications form, and what the conditions are for their occurrence, persistence, and enlargement are in progress in this laboratory.

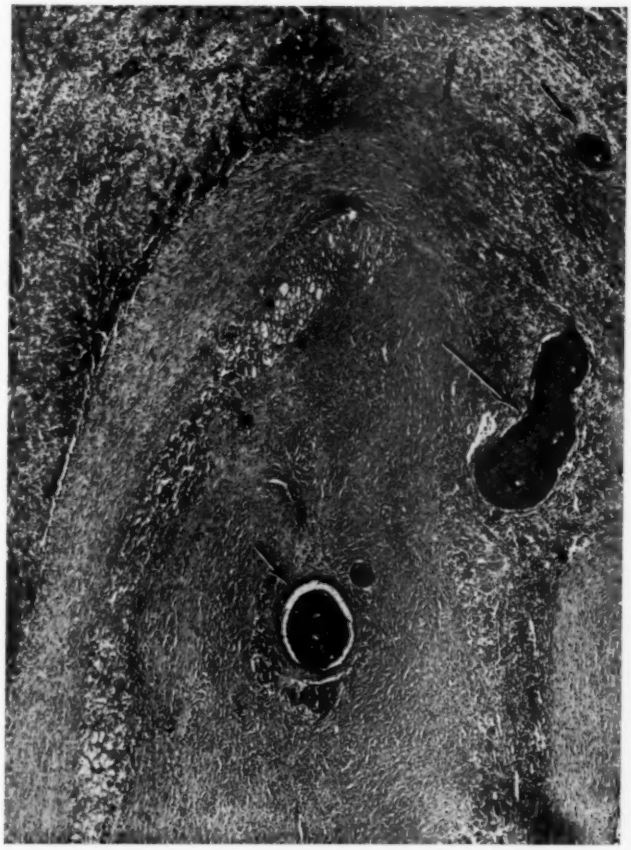

Fig. 6.—Large vascular bridge distended with radiopaque mass (*long arrow*) crossing endocardium of scarred trabecula carnea into organized part of thrombus. Injected vessels in center of trabecula carnea and in substance of thrombus (*short arrows*). (Hematoxylin-eosin, ×35; reduced ⅓.)

Anatomically, these communications seem to allow blood flow either from the coronary arterial tree or from the cardiac lumen. Since obliteration or regression of vessels is generally recognized to follow cessation of blood flow, the fact that in some instances these communications were large and appeared to have persisted long after the organization of the thrombus was complete would indicate that such a flow does occur in vivo, and to an extent beyond the requirements of the organization process. The topographic relationship which these

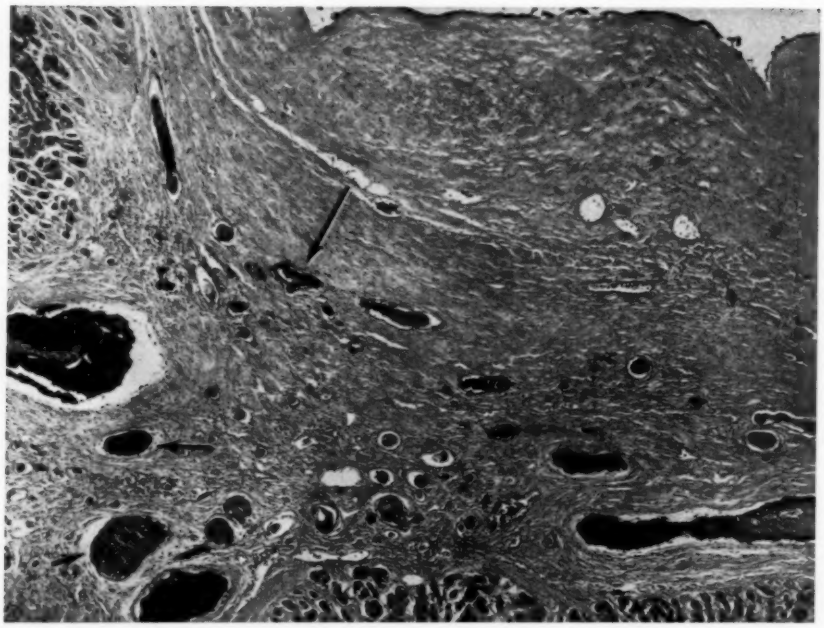

Fig. 7.—Completely organized thrombus, showing vessels filled with radiopaque mass introduced into coronary arteries (*short arrow*); with India ink introduced into ventricular cavity (*medium arrow*); and with mixture of ink and mass (*long arrow*). Large pools of ink and mass which abut on sides of photograph are extensions of cardiac lumen. Parts of myocardium and cardiac lumen are also shown. (Hematoxylin-eosin, ×90; reduced ⅓.)

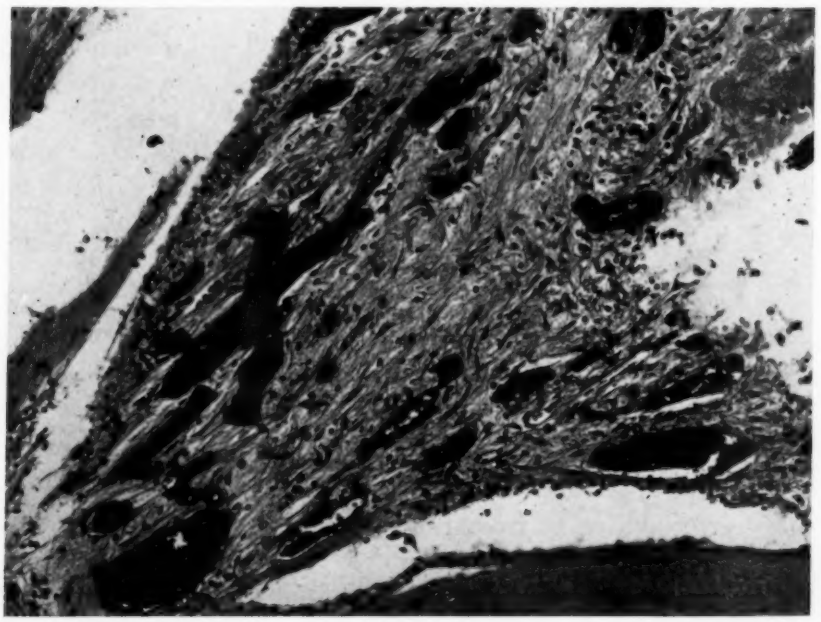

Fig. 8.—Base of organizing thrombus, showing newly formed vessels distended with India ink introduced into ventricular cavity. Portion of original endocardium is shown at bottom and left sides of photograph. (Hematoxylin-eosin, ×340; reduced ⅓.)

communications bear to areas of the myocardium with a patently depleted coronary blood supply favors the contention that, at least in certain phases of the cardiac cycle, the direction of this flow is from the lumen of the left ventricle.

The formation of endocardial thrombi is a common sequel of myocardial infarction and is regarded as harmful, since the thrombus often gives rise to emboli. From this study, it would appear that the thrombus may also play the beneficial role of providing new vessels to usher blood from the cardiac lumen to the myocardium. Subsequent to infarction, such a vicarious blood supply may contribute in some measure to a more rapid healing of the infarct in its later stages, and to the improvement of the circulation to the myocardium in the periphery of the infarcted area.

Fig. 9.—Portion of angiogram of unrolled heart showing absence of injected arteries in lower part of left ventricle with healed infarct to which old thrombus is attached (*arrow*). The coronary arteries are stenosed but patent up to the zone beneath the thrombus. Calcific densities in mitral and aortic valvular rings. (Positive print, ×1; reduced ⅓.)

The findings also indicate that segments of the communicating channels between the lumen of the left ventricle, the thrombus, and the coronary system may fail to form or may become closed off. In one instance, channels leading from the cardiac lumen extended no farther than the confines of a recent thrombus; organization of the clot apparently proceeded with the blood supply derived solely from the cardiac lumen. In another instance, vascular elements were found in the substance of a completely organized thrombus, but no vascular communications with the cardiac lumen or the coronary system could be demonstrated. Here, the possibility was entertained that with the completion of organization, vascular segments which linked vessels of the thrombus to the cardiac lumen or the coronary system had become obsolete and, therefore, regressed. In 3

other hearts, the vascular bed of parts of the cardiac wall vicariously supplied from the lumen of the left ventricle appeared to have become sequestrated from the coronary arterial tree. In these specimens, a zone of coronary arterial branches which was inaccessible to Schlesinger's mass from the coronary ostia was found beneath old thrombi. Islands of surviving myocardium within the zone bore witness to the existence in vivo of some blood supply to the area. Conceivably, arterial blood may have reached the zone from one or both of two sources: from the main coronary arteries through vessels with calibers less than 40 micra, and directly from the lumen of the left ventricle through Thebesian veins and vessels of the old thrombus. The concept that the myocardium may survive total loss of both coronary and intercoronary collateral circulations is supported by 2 cases described by Leary and Wearn,[6] in which complete occlusion of both coronary orifices produced no ischemic damage to the myocardium.

Certain practical implications may be drawn from this study. The demonstration of naturally acquired vascular communications between the lumen of the left ventricle and the vessels of the myocardium would seem to warrant further investigations to determine: (a) whether the formation of such communications can be artificially induced, and (b) whether a significant augmentation of the blood supply of ischemic hearts with diseased coronary arteries would then result.

SUMMARY AND CONCLUSIONS

A histologic and injection study of vascularized cardiac thrombi associated with infarcts in the left ventricle of human hearts is presented and the following conclusions reached: (1) Vascular communications may form between the lumen of the left ventricle, the vessels of the organizing thrombus, and the coronary system. (2) Such communications may persist in old thrombi. (3) Those persisting can be of substantial size, and extend as such into the coronary arterial tree. (4) These communications may serve to usher blood from the cardiac lumen to the myocardium. (5) The vascular bed of parts of the cardiac wall vicariously supplied from the lumen of the left ventricle may become sequestrated from the rest of the coronary system.

Injected specimens were prepared by Sandra J. Fish, A.B. Walter H. Abelmann, M.D., Assistant Professor of Medicine, Harvard Medical School, and Assistant Physician, Thorndike Memorial Laboratory, Boston City Hospital, read the manuscript critically and offered helpful suggestions.

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A-V Nodal Parasystole

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Although ventricular parasystole is no rarity, supraventricular forms are uncommon. In a previous paper, two observations on atrial parasystole were described[9] and a few instances of this arrhythmia which had been reported by others were discussed. Some of these arrhythmias designated as atrial parasystole seemed, on further study, to represent a parasystole originating in the A-V node. Within the last fourteen months we have collected four additional instances of A-V parasystole. In the present paper these observations will be described for the first time as an entity.

OBSERVATIONS

Observation 1.—This 58-year-old man with an inferior wall myocardial infarction presented an A-V nodal parasystole for several weeks during his illness.

Fig. 1 shows a long strip of tracing taken in Lead II which is divided into three sections for the purpose of reproduction. Ectopic atrial beats with deeply inverted P waves occur in different phases of diastole. The sinus rate is about 70 beats per minute. The P-R intervals of the sinus beats and of the ectopic beats, when they appear late in diastole, measure 0.14 second. Since the P waves of the ectopic beats are low positive in Lead I and deeply inverted in Leads II and III, they unquestionably originate in the upper portion of the A-V node (coronary sinus area).

The intervals between the ectopic beats, which measure 387, 385, 375, 376, 386, 375, and 375,* correspond to an ectopic rate of 15 beats per minute. It is probable, however, that the actual rate of impulse formation in the ectopic center is a multiple of 15, and some of the ectopic beats are blocked when they appear during the refractory phase of a sinus beat. The constant length of the interectopic intervals, as well as the occurrence of the ectopic beats in different parts of the diastole, speak for parasystole.

The appearance of combination or summation beats further characterizes parasystole. In Fig. 1,*D*, registered subsequently in the same patient when the sinus rate was 83, the second and last P waves show the summation of a sinus and an ectopic P wave. This pattern results if an ectopic impulse is formed while a sinus beat spreads over the atria so that both impulses activate parts of the atria.

In the presence of summation, exact measurement of the interectopic interval is impossible because the beginning of the ectopic P cannot be ascertained. Thus, in Fig. 1,*D* the second interval measures exactly 376, whereas the other two intervals involving summation beats can only

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*These figures represent hundredths of a second throughout.

be approximated as 186 and 382. Since 186 is about one half of the other intervals, one may assume that the intervals of double length are caused by the appearance of some ectopic impulses during the refractory phase.

Another combination beat appears toward the end of Fig. 2,*B*. These tracings were obtained two weeks after Fig. 1,*D*. The sinus rate is 90 beats per minute, with slight variations. As before, the inverted P waves appear in different phases of diastole; those which appear early in diastole are aberrantly conducted to the ventricles. In Fig. 2,*A* the successive P-P intervals of the ectopic beats measure 182, 185, 183, 182, 179, 178, and 179. In Fig. 2,*B* the interectopic intervals are 176, 719 (4 × 180), and 183.

During carotid pressure the rate of the parasystolic center is slowed considerably. This is illustrated in Fig. 2,*C*, in which three ectopic beats appear at intervals of 215 and 210. During another application of carotid pressure, the intervals were 280 and 260. Carotid pressure did not influence the rate of the ectopic center in the observation by Gentile.[3]

These tracings show that the length of the interectopic interval actually is about 186 (rate 32), and that the intervals of double length are found because ectopic impulses arise at a time when the atria are refractory after a sinus beat.

Observation 2.—In this 67-year-old woman with osteoporosis who failed to show evidence of cardiac disease, the electrocardiogram revealed essentially normal ventricular complexes. Premature atrial contractions appeared in different phases of diastole. These contractions exhibited the low positive P waves in Lead I, and inverted P waves in Leads II and III, which typify premature A-V beats. During sinus rhythm with a rate of 90 the premature beats showed a P-R interval of 0.10 second; the normal P-R interval was 0.12 second.

In Fig. 3,*A*, four ectopic beats in Lead II are separated by intervals of 80, 325, and 331. On another day, with the same sinus rate of 90, the interectopic intervals were 246 (3 × 82), 83, 254 (3 × 84.5), and 338 (4 × 84.5) (Fig. 3,*B*). In Lead III (Fig. 3,*C*), with a sinus rate of 69, the P-P intervals were 309 (3 × 100.3), 212 (2 × 106), and 300 (3 × 100). These measurements indicate that the parasystolic center produced an ectopic rate of about 75 when the sinus rate was about 90, and a rate of about 60 when the sinus rate was 69.

Observation 3.—The third case in this series is a 68-year-old retired importer with a known right bundle branch block of seven years' duration. In addition to a presumed coronary sclerosis he has had chronic bronchitis, a mild pulmonary emphysema, and a duodenal ulcer. His electrocardiogram presented a sinus rate of 51, sinus beats with a P-R interval of 0.14 second, and premature beats with a P-R interval of 0.12 second showing low positive P waves in Lead I and inverted P waves in Leads II and III. These complexes not only reveal an origin in the A-V node but display a varying relationship to the preceding sinus beat as in parasystole.

Fig. 4,*A*, recorded in Lead II, includes five such premature beats. Two ectopic beats follow each other directly on two occasions, with interectopic intervals of 140 and 147. Otherwise the interectopic intervals measure 147, 140, 432 (3 × 144), and 147. In this strip of tracing the ectopic rate may therefore be calculated as 42 beats per minute.

Strips *B* and *C* of Fig. 4, which were obtained six days later, are continuous and present a single summation beat (the fifth P wave of *B*); the sinus rate is 57 and the interectopic intervals measure 134, 150, 281, 402 (3 × 134), 412 (3 × 137), 280, 130, 380 (3 × 127), and 128. In *D*, during carotid pressure the interectopic intervals increase from 178 to 366, 374, and 346.

In this patient, as in our other observations on patients with A-V nodal parasystole, the parasystolic rate increased with the sinus rate, and carotid pressure slowed the parasystolic rhythm.

Observation 4.—This 73-year-old woman had a mild hypertension associated with diabetes and coronary sclerosis. The electrocardiogram showed a typical A-V nodal parasystole. Ectopic beats with varying coupling exhibited low positive P waves in Leads I and aV_R, and deeply inverted P waves in Leads II, III, and aV_F. In addition, the interectopic intervals were constant, and summation or combination beats occurred often.

Fig. 5,*A* presents in Lead aV_F a sinus rate of 75. Ectopic beats appear in different phases of diastole, with interectopic intervals of 235, 238, 240, 238, and 240. The interectopic interval is most probably 117-120 (rate 50), but every second ectopic impulse is blocked because the atria are still in the refractory phase after a sinus beat.

Fig. 1.—Observation 1. The first three tracings (*A-C*) are continuous; they represent Lead II. The ectopic inverted P waves appear in different phases of diastole, and the interectopic intervals measure 375 to 387 hundredths of a second. In *D* the second and the last P waves show summation of ectopic and sinus impulses. The ectopic P waves appear at regular intervals of about 186 hundredths of a second.

Fig. 2.—Observation 1. Parasystole with aberrant intraventricular conduction of the premature ectopic beats in *A* and *B*. A combination beat appears in the last third of *B*. The interectopic intervals are about 180 hundredths of a second. Carotid pressure (*C*) slows not only the sinus rhythm but also the ectopic rhythm. The pressure is indicated by the thin black line at the bottom of *C*.

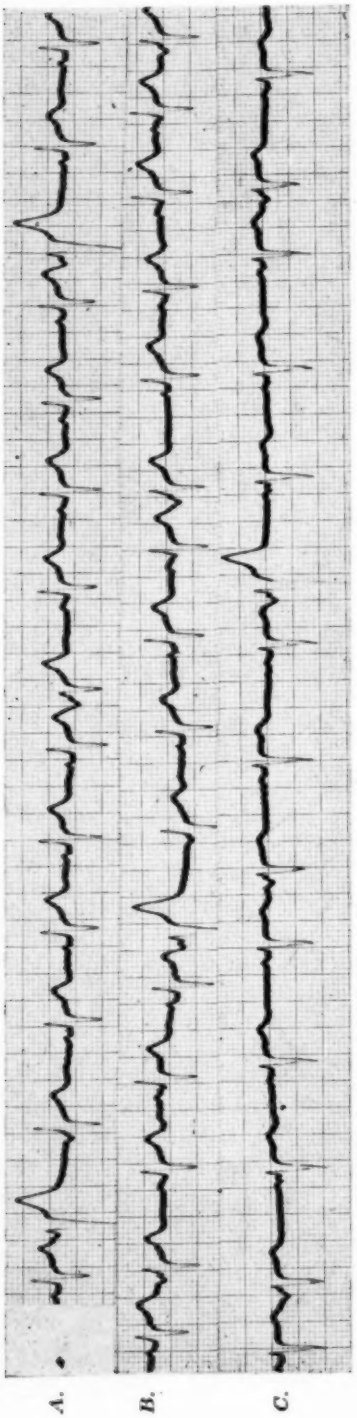

Fig. 3.—Observation 2. Interference between a sinus rhythm and an ectopic A-V rhythm. *A* and *B*, Lead II; *C*, Lead III. The ectopic beats appear in different phases of diastole. In *A* and *B*, two ectopic beats follow each other in succession.

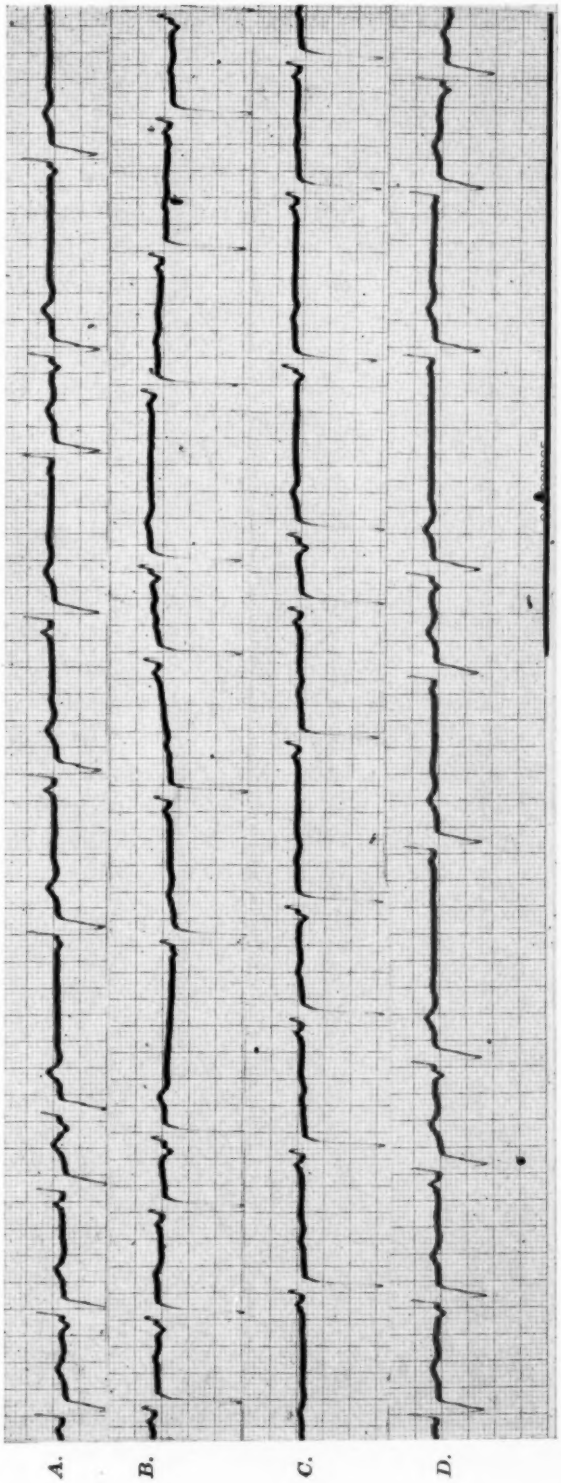

Fig. 4.—Observation 3. *A* and *D* were recorded in Lead II; *B* and *C* in Lead III. *B* and *C* are continuous. A slow sinus rate interferes with a slower ectopic A-V nodal center. On several occasions, two ectopic beats follow each other directly (*A* and *B*). A summation beat is seen in *B*. Carotid pressure increases the ectopic interval (*C*).

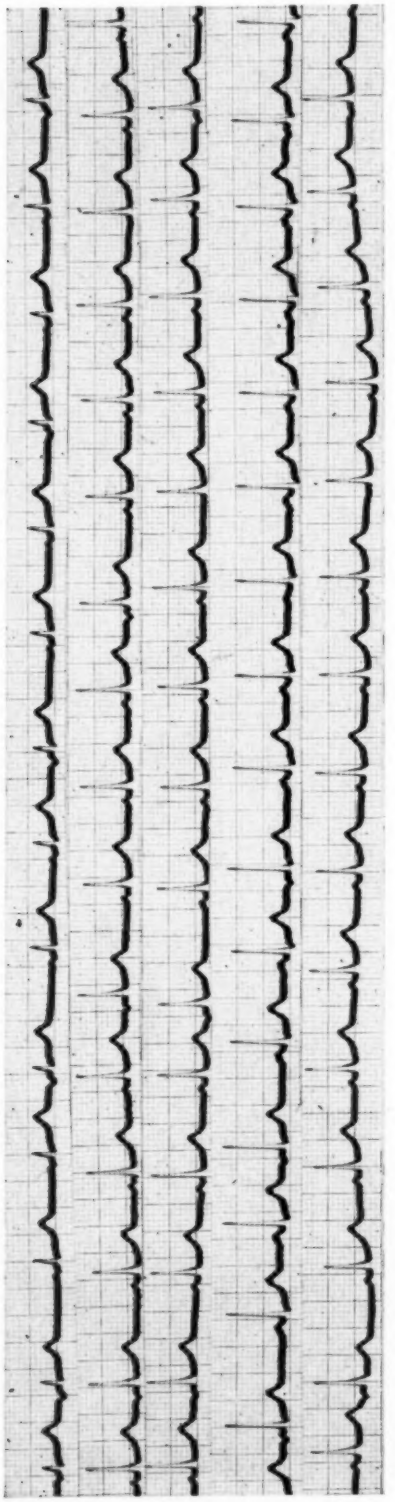

Fig. 5.—Observation 4. *A* is a tracing recorded in Lead aV_F; *B-E* were recorded in Lead II. Ectopic A-V nodal beats appear in different phases of diastole and are separated by regular interectopic intervals. Summation beats appear in all leads.

Fig. 5,*B* records in Lead II a sinus rate of 81-85, interectopic intervals of 286, 286, and 294, and a summation beat (the third from the last). The ectopic rate is about 40 per minute. In Fig. 5,*C*, the sinus rate remains unchanged and the intervals are 280, 382, 284, and 280. One combination beat appears. In Fig. 5,*D*, with a sinus rate of 88, the intervals measure 214, 208, 208, 212, and 340. Fig. 5,*E* shows interectopic intervals of 673 (5 × 135), 284 (2 × 142), and 286, and includes two combination beats.

DISCUSSION

These observations present a collection of supraventricular parasystole originating in the A-V node. Not only are ectopic beats of varying coupling recorded at intervals having a common denominator, but in this arrhythmia, positive ectopic P waves appear in Lead I and negative ectopic P waves in Leads II and III. As in ventricular parasystole, combination beats occur, which result whenever the sinus and the A-V node simultaneously activate parts of the atria.

The sinus and ectopic rhythms, however, are not completely independent as in ventricular parasystole. Frequently the statement is made that in atrial parasystole the sinus node must be protected from the ectopic impulse. This is incorrect, because the ectopic impulse usually enters the sinus node and excites it. Consequently, the ectopic and sinus rhythms join to form a pattern of interference which is repeated many times. The presence of two rhythms has also been described in instances of block between both atria. These rhythms originate, however, in centers located in different chambers which contract independently. In A-V nodal parasystole both rhythms involve both chambers.

Dissociation with interference, on the other hand, requires differential consideration. In interference between the sinus and the A-V node the latter is not protected as in A-V parasystole. The conducted sinus impulse breaks into the A-V center, which then must form stimuli anew. Thus, whenever the sinus beat is conducted to the ventricles, the two rhythms are coupled. In A-V parasystole, on the other hand, repetition of a pattern of interference occurs.

When the pattern of A-V parasystole was recognized in these tracings, we reviewed previously reported cases of atrial parasystole. In three instances we found A-V nodal parasystole which had been interpreted by the authors, including ourselves, as atrial parasystole. One observation by Attinger on an 84-year-old woman exhibits low P waves in Lead I and deeply inverted P waves in Leads II and III. Although usually regarded as signifying an atrial parasystole, the ectopic beats obviously originated in the A-V node. Likewise, the observations of Vedoya (Observation 5) and Gentile (Observation 2) undoubtedly represent an A-V parasystole. Finally, in a previously published instance of parasystole by Scherf and Boyd the ventricular complexes of the parasystolic center had the same form as those of sinus origin. In this observation we may postulate an ectopic focus above the bifurcation, possibly in the A-V node, with block of the retrograde conduction.

In a study on parasystole, Pick describes a patient with A-V nodal parasystole with a sinus rhythm of 59 and an A-V rhythm of 55. An instance of A-V nodal parasystole can be seen in Figure 125 of the monograph by Katz and Pick.

TABLE I

AUTHOR	RATE OF SINUS RHYTHM	RATE OF ECTOPIC CENTER
Attinger[1]	85	40
Vedoya[10]	92	50
Gentile[3]	70–79	57
	82	69
	72	61
Pick[5]	59–60	55
Scherf and Boyd[8]	78	42
Present study		
Observation 1.	70	30
	90	33
Observation 2.	90	75
	69	60
Observation 3.	51	42
Observation 4.	75	50
	81–85	40

Table I shows the rates of sinus rhythm and ectopic rhythm in five instances of A-V parasystole previously published and in our four recent observations. The rates, with one exception (our Observation 2), are remarkably slow. A slow ectopic rate is the rule in ventricular parasystole but is an unexpected finding in atrial and A-V nodal parasystole. In the ventricular form the slow rate is presumed to occur because the ectopic center is protected from the sinus rhythm ("protection block"). Since the center is independent, it develops its own autorhythm, which is inherently slow. The inherent automaticity of the atrial and A-V nodal centers, however, is relatively fast. Therefore, the slow rate in three of our observations and in those reported before is striking. Of course, a slow rate would result if the real interectopic interval were to be lengthened by a 2:1 or 3:1 exit block. Another explanation for the slow rate is that in A-V nodal parasystole we are not dealing with a normal automaticity, but with an abnormal impulse formation in the "protected" center. Protection, at best, is a concept difficult to explain. In previous studies[2,8] we indicated that proof was lacking for the original conception of a block area surrounding a center, and offered alternative reasons for the inability of the center to respond. One explanation for the fact that the ectopic center is not disturbed by the spread of the normal impulse is that of a rapid ectopic stimulus formation. Experimental studies indicate that if the center is rapidly active, extraneous impulses fail to disturb it.[6] If this mechanism is present, the directly measured and calculated interectopic intervals are a multiple of the actual ones because of 2:1 or 3:1 response.

In our Observation 1 the registration of long tracings enabled us to measure the refractory phase of the atria for the parasystolic impulse. The earliest ap-

pearance of a parasystolic P following a normal P is after 0.40 second. This corresponds closely to previous measurements of 0.49 and 0.46 second in patients studied by Vedoya and Gentile.

Ventricular parasystole is usually encountered in abnormal hearts, and its presence alone should make one suspicious even if no other indications of cardiac disease exist.[2] In two of the observations reported in the present paper, and in those of others,[3,10] the heart was apparently normal. More experience will be required before the statement is permitted that A-V nodal parasystole may appear in the healthy heart.

Protection of A-V nodal centers from impulses conducted from atria to ventricles has been observed in experiments on dogs.[7]

SUMMARY

Four instances of parasystole with the ectopic center in the upper portion of the A-V node are described, and several similar observations were collected from the literature.

The astonishing fact is stressed that the automaticity of the ectopic center is slow in most of these observations.

Unlike ventricular parasystole this form seems to appear in persons with healthy hearts.

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Epicardial Low-Frequency Tracings of the Left Atrium. A Comparison With the Preoperative Esophageal Pulse in Mitral Defects

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Esophageal piezocardiograms have been interpreted as recording the pulsations, at different levels in the esophagus, of small areas of the heart chambers, namely, the left ventricle (lower records) and the left atrium (middle and upper records).[1-5]

The utilization of this procedural technique in the close examination of patients with mitral defects increases the importance of an investigation of the origin of the pulsations recorded in these tracings. In an attempt to verify whether esophageal piezocardiograms are a true reproduction of the pulsations of the left atrial wall, low-frequency tracings have been recorded directly from the atrial epicardial surface and compared with those obtained in the esophagus. Furthermore, an attempt has been made to establish the relationship between the different patterns and the type of surgically proved mitral lesion, in order to evaluate the diagnostic importance of these patterns.

METHODS

Esophageal piezocardiograms have been recorded preoperatively, at different levels in the esophagus, by means of a tube with a rubber balloon at the terminal end. The balloon is 2.7 mm. in length, 8 mm. in width, and 2/10 mm. in thickness. The lumen of the tube is 1 mm.[4] Epicardial tracings have been obtained with the same apparatus, the balloon having been inserted into a special container (Fig. 1) and placed by the surgeon on the epicardial surface of the left atrium after the pericardium was opened. Curves have been recorded from the auricular appendage and the lateral and superior walls. In a few cases, additional pressure curves were obtained during surgical exploration, by directly inserting the balloon connected with an air-filled electromanometer into the left atrium,[6] or by puncture of the atrial wall with a needle connected with a water-filled electromanometer.

Twenty-one patients were examined. Technical difficulties did not allow in all instances the recording of epicardial tracings in the three different areas of the atrium. Surgical exploration was performed on all the patients, and revealed pure mitral stenosis in 13 of them and an associated variable degree of mitral insufficiency in 8. In no instance were significant additional defects of other valves detected.

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RESULTS AND COMMENTS

Relationship Between Esophageal and Epicardial Recordings.—On the whole, a remarkable similarity was found between the esophageal curves and the left atrial epicardial tracings in records from the same patient (Table I). This coincidence was shown by 16 of the 21 patients examined and is of statistical significance. In only 2 cases were the curves completely dissimilar, whereas in the other 3 cases, similar patterns were revealed in only a few beats.

TABLE I

	PRESENT	ABSENT	TOTAL	P
Similarity between esophageal and epicardial recordings	16	5	21	<0.05
Coincidence between esophageal pattern and surgical finding	15 MS = 8 MSI = 7	6 MS = 5 MSI = 1	21	<0.06

MS: Mitral stenosis. MSI: Mitral stenosis with insufficiency.

In the 16 patients with similar recordings, a perfect coincidence between esophageal and epicardial tracings was often found. Figs. 2 and 3 show two cases from which we can draw some general observations: (1) The similarity of the esophageal and epicardial curves is more apparent when more extensive recordings are made from both the esophagus and the epicardial surface. (2) The similarity is more remarkable still when the recordings are derived from nearly the same point. (3) Special emphasis is to be placed on the pattern obtained from the auricular appendage before its amputation, since this pattern was the most similar to the esophageal recordings and the most reliable from the diagnostic point of view.

As to the 5 cases which did not show a close similarity of the recordings, a number of circumstances which could invalidate their correlation need to be briefly mentioned: (1) Failure to obtain satisfactory tracings both in the esophageal and the epicardial recordings. (2) Failure to obtain both recordings from the same point for proper correlation. It must be added that in no instance could the posterior wall of the atrium be reached by the balloon during the epicardial examination: it is obvious that esophageal recordings usually reflect the pulsations of this wall. (3) Rapid or very irregular rhythm, which could significantly alter the pattern, as shown in Fig. 4. During tachycardia a considerable reduction of the ventricular filling and the systolic output occurs, causing a diminution in systolic regurgitation. The additional impediment to atrial emptying results in an extreme atrial hypertension (atrial tamponade). This condition may simulate mitral stenosis in patients with combined mitral stenosis and insufficiency, the recognition of regurgitation being obscured.[7,8] (4) Additional hemodynamic changes as a consequence of operation; these were revealed by a fall in blood pressure, sometimes to 80 mm. Hg. (5) Large left atrial clots which produce rigidity of the wall.

Relationship Between Esophageal and Epicardial Patterns and Surgical Verification of Mitral Lesions.—On the basis of previous observations, certain criteria have been developed for the diagnosis of mitral defects by means of the esophageal piezocardiogram.[1,4,5,7,9,10]

In cases of pure mitral stenosis, various patterns can be found, but in most of the cases the curve has a plateau-like form during ventricular systole, sometimes showing a moderate decrease after the early systolic peak or a variable downward deflection with a steep rise followed by a late plateau, which never reaches the amplitude of the protosystolic peak.

The recognition of mitral insufficiency is based on the evidence of a late systolic or protodiastolic "V" wave of greater amplitude than the initial peak, with a slight ascending limb and a rapid fall (Fig. 5).

In the epicardial tracings, both the plateau-like and the late systolic wave curves were obtained more clearly from the auricular appendage, respectively in cases of mitral stenosis and of mitral stenosis and insufficiency.

A comparison of the different patterns with the surgically proved mitral defects demonstrated that 8 cases out of 13 with mitral stenosis showed esophageal and epicardial curves with the characteristic features of this lesion. In 1 case a technical error was considered, whereas in 4 cases the tracings had the features

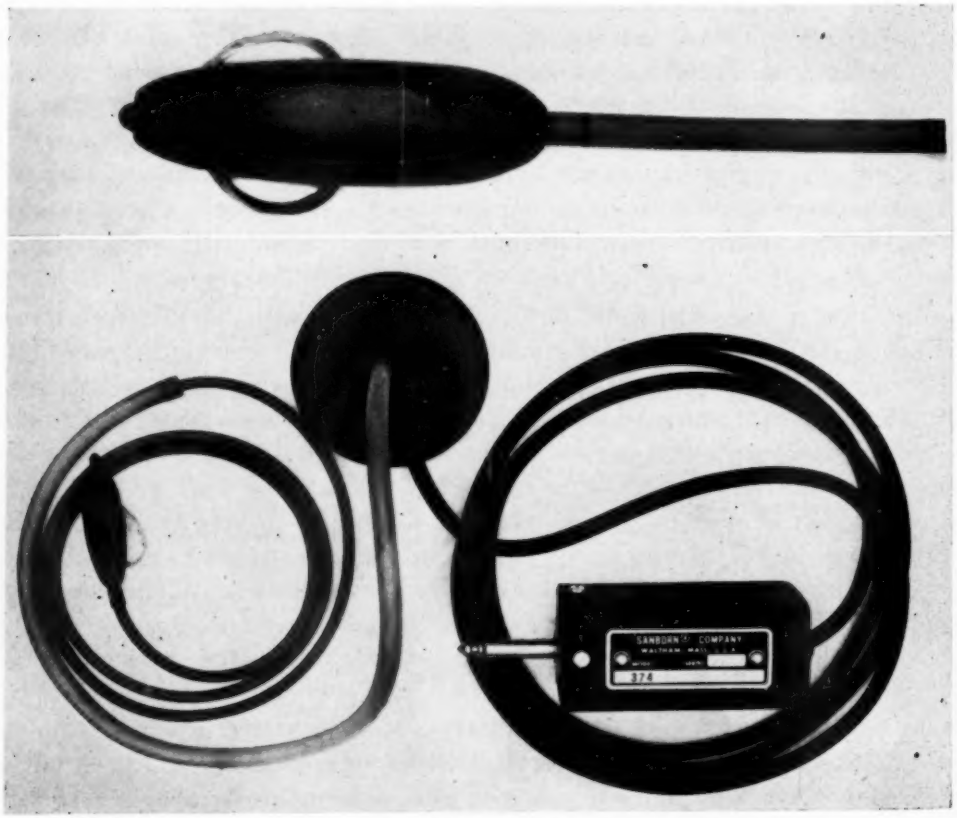

Fig. 1.—Apparatus for epicardial low-frequency records. The balloon for esophageal recordings has been inserted in a red galalith container (*Upper:* actual size).

of both stenosis and insufficiency. In one of them the preoperative esophageal curve showed some regurgitation and a heart rate of 75; during operation the heart rate rose to 140, and there was no evidence of mitral insufficiency either during surgical exploration nor in the epicardial pattern. Another patient had a loud systolic murmur which radiated to the axilla before operation; after commissurotomy, surgical verification showed evidence of mitral regurgitation. The third case had an apical systolic murmur. In the fourth case, mitral stenosis was not of severe degree (2.5 cm.^{2}), and fibrosis of the valve leaflets was found. On the basis of these observations, it must be concluded that no absolute value should be given in all cases to the surgical findings.

All but one of the 8 patients with mitral stenosis and insufficiency showed esophageal and epicardial patterns of mitral insufficiency. The one who had curves of mitral stenosis showed a hemodynamically insignificant regurgitation in addition to a severe mitral stenosis.

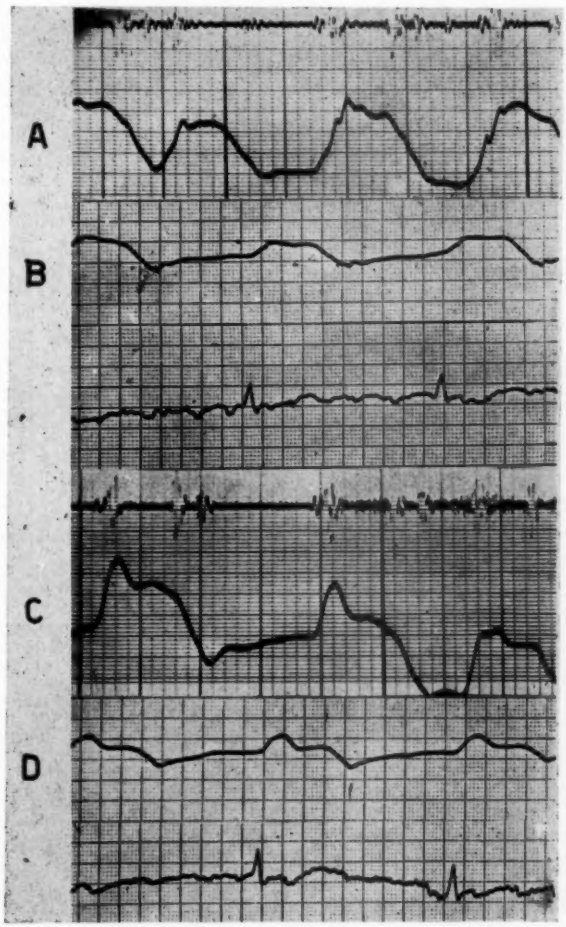

Fig. 2.—Patient with pure mitral stenosis. Atrial fibrillation. Curves at different levels from the esophagus (*A*, lower level; *C*, upper level), showing similarity with atrial epicardial recordings from the lateral wall (*B*) and the superior wall (*D*), respectively.

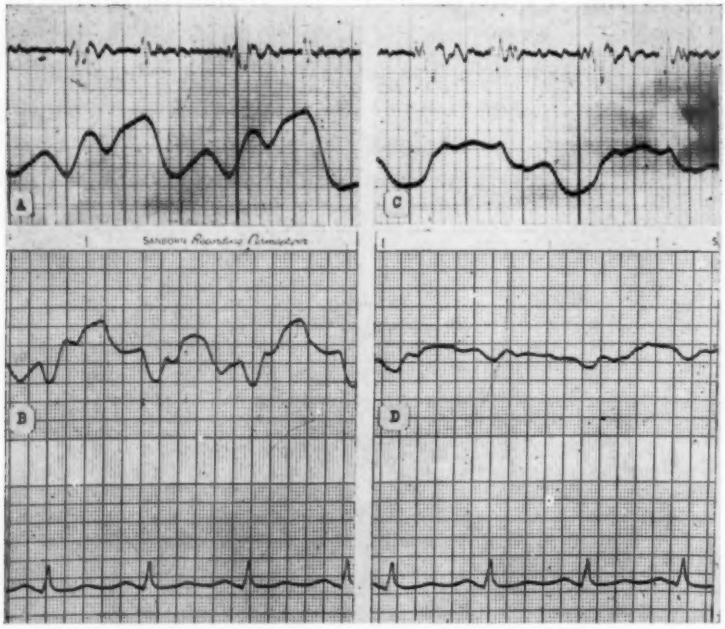

Fig. 3.—Patient with mitral stenosis and moderate insufficiency. Sinus rhythm. Esophageal curves (*top*) and epicardial tracings (*bottom*). Remarkable similarity between the esophageal pattern in *A* and the epicardial tracing from the left auricle (*B*).

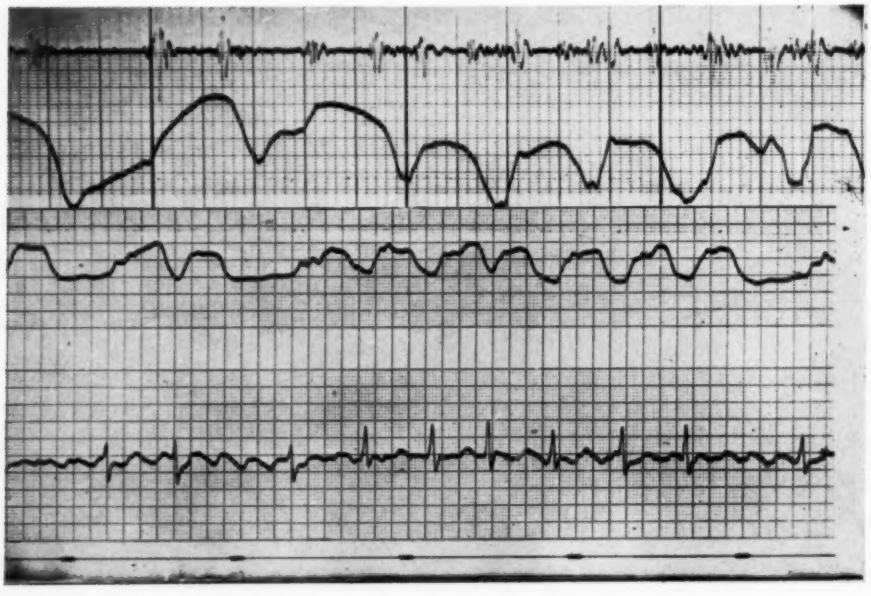

Fig. 4.—Patient with mitral stenosis and insufficiency. Atrial fibrillation with rapid ventricular rate. Esophageal piezocardiogram (*top*) and epicardial curve from the left auricle (*bottom*). In both tracings the pattern of mitral insufficiency is recorded on a few beats following long diastole. Note the plateau-like pattern of mitral stenosis after short diastole.

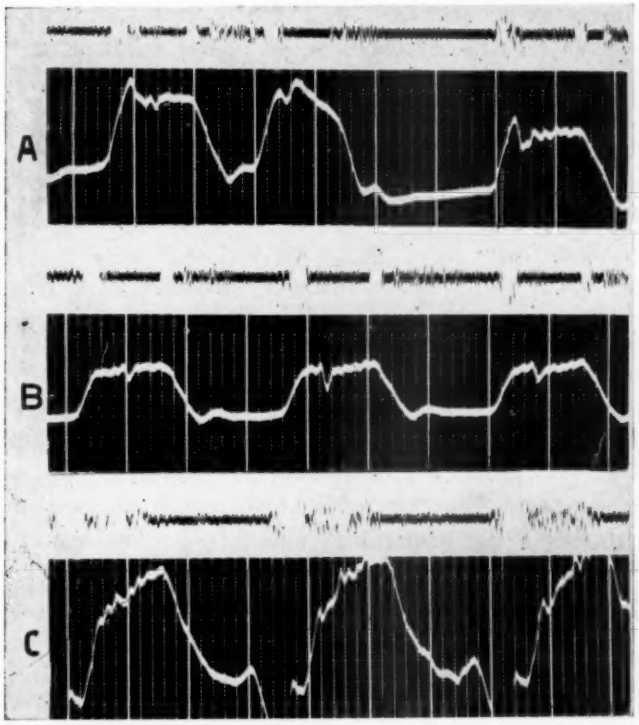

Fig. 5.—The pattern of pure mitral stenosis (*A*), mitral stenosis with moderate insufficiency (*B*), and pure mitral insufficiency (*C*) in the esophageal piezocardiogram.

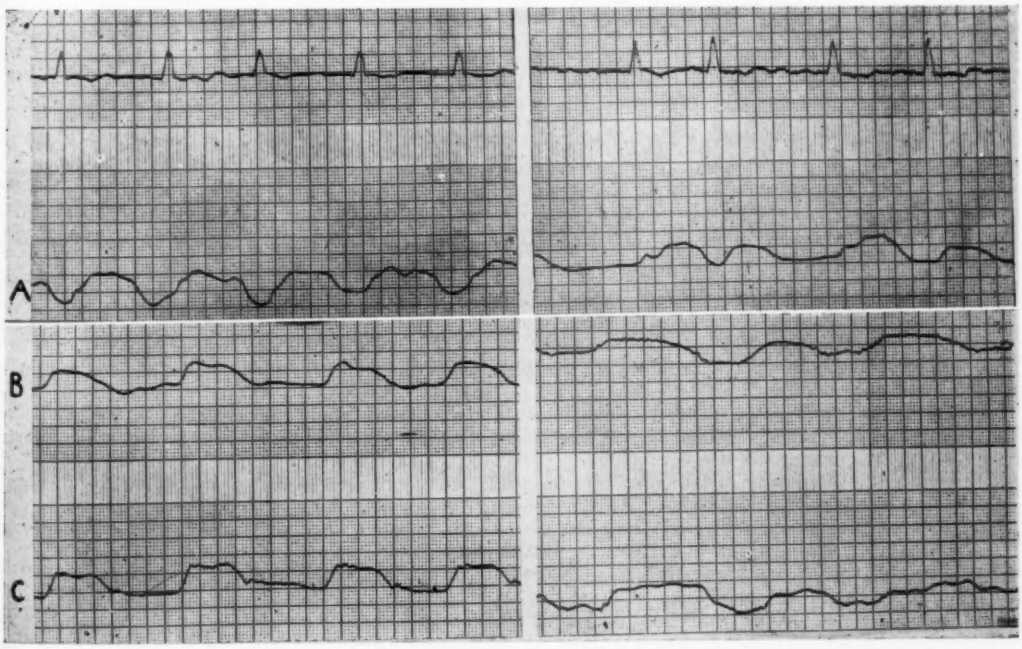

Fig. 6.—Patient with pure mitral stenosis in whom a moderate insufficiency was caused by commissurotomy. Recordings before (*left*) and after (*right*) commissurotomy. *A*, Esophageal curve. *B*, Epicardial tracing. *C*, Atrial pressure curve.

The atrial pressure records obtained in a limited number of cases have confirmed other observations.[8] Whereas in some cases—most often those with mitral regurgitation—they were perfectly similar to the esophageal and the epicardial patterns, in other cases no coincidence has been found (Fig. 6). This dissimilarity does not appear to be dependent on the rise in atrial pressure. It may probably be related, in turn, to the distensibility of the atrial walls, the pulse pressure, the myocardial conditions of the left atrium, and some other factors which are still unknown.

SUMMARY AND CONCLUSIONS

A comparative study of esophageal piezocardiograms and epicardial low-frequency curves recorded from the left atrium has been made in 21 cases, and the data have been correlated with the surgical verification of mitral defects.

A close similarity has been found between esophageal and epicardial records in most of the cases: special emphasis was placed on the contour of the tracings obtained from the auricular appendage, since these tracings appeared to be the more reliable from the diagnostic point of view.

We have found that, by means of the esophageal piezocardiogram, curves of certain and absolute atrial origin may be obtained. Their importance in the study of atrial dynamics in patients with mitral defects is apparent. However, in the evaluation of mitral lesions, it is well to bear in mind the possibility that the contour of the curves may be altered by some clinical, hemodynamic, or pathophysiologic conditions, such as tachycardia, fall in blood pressure, atrial clots, and distensibility of the atrial wall.

Finally, it has been confirmed that the pulsations of the atrial wall are not always related to changes in left atrial pressure.

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The Electrocardiogram, Spatial Vectorcardiogram, and Ventricular Gradient in Congenital Ventricular Septal Defect

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INTRODUCTION

The electrocardiogram (ECG) in ventricular septal defect has been a subject of controversy in the medical literature for a number of years. Taussig,[1] as well as others,[2,3] considered the ECG to be of little diagnostic importance and regarded it as normal in most instances. Other investigators have assigned various degrees of diagnostic importance to the electrocardiogram in this defect. Marsico and associates,[4] employing the concepts of Cabrera and Monroy,[5] asserted that the most important electrocardiographic findings in ventricular septal defect were a pattern of systolic overloading of the right ventricle (rR′, R, Rs, qR in Lead V_1) and diastolic overloading of the left ventricle (tall, peaked T waves in Leads V_5 and V_6). These same authors emphasized the deep Q wave seen in Lead V_6 and considered it to be the result of septal hypertrophy. Wood and associates[6] stated that in ventricular septal defect there was a conspicuous Q wave and a tall R wave in Lead V_6 which indicated left ventricular hypertrophy (LVH), and a secondary R wave with an inverted T wave in Lead V_1 which suggested right ventricular hypertrophy (RVH). Carlotti[7] considered the ECG in ventricular septal defect to resemble that seen in atrial septal defect. Zimmerman and associates[8] noted an RSR′ pattern in Lead V_1 in patients with moderate elevation of right ventricular systolic pressure and right ventricular hypertrophy, whereas in patients whose pulmonary arterial pressure approached the systemic arterial pressure they found flattened T waves in the left-sided precordial leads. Mannheimer and co-workers[9] were of the opinion that there was left ventricular hypertrophy in patients with low right ventricular pressure, and right or combined ventricular hypertrophy in patients with high right ventricular pressure. Burchell[10] pointed out that when the ECG displayed left ventricular preponderance, the prognosis at surgery was better than when right or combined hypertrophy was present. Other investigators[11] have reached similar conclusions. Katz and Wachtel[12] described an electrocardiographic manifestation in patients with

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congenital heart disease which consists of large diphasic complexes in the precordial leads to the left of the transition zone. Others have noted this phenomenon in ventricular septal defect, the reported incidences being 31,[4] 72,[13] 60,[14] 53,[15] and 10 per cent.[16]

Fyler and co-workers,[11] in an anlysis of 272 electrocardiograms from 98 children with ventricular septal defect, found only 9 instances of left axis deviation (0° to −30°), whereas right axis deviation (+90° to +180°) was present in 31 instances. Over half of the patients had normal axis deviation (0° to +90°). An rSr′ or rsR′ pattern was present in the ECG of 54 patients. The above series included 17 patients who had pulmonary stenosis in addition to the ventricular septal defect.

Char and associates[13] found no typical pattern in the ECG in ventricular septal defect; however, they noted that right ventricular hypertrophy was present in the majority of the patients and that the T waves in Lead V_1 were usually

TABLE I. VARIOUS ELECTROCARDIOGRAPHIC MANIFESTATIONS ACCORDING

AGE	NUMBER OF PATIENTS	Q WAVE IN LEAD V_1 OR V_2	DIPHASIC P WAVE IN LEAD V_1 OR V_2	P WAVE <2.3 MV. IN LEAD II OR III	MEAN P-R INTERVAL (SEC.)	P-R INTERVAL PROLONGED	INTRINSICOID DEFLECTION IN LEAD V_1 DELAYED*	INTRINSICOID DEFLECTION IN LEAD V_6 DELAYED†	MEAN QRS DURATION (SEC.)	COMPLETE RBBB
0–1	21	1 (5%)	14 (67%)	4 (19%)	.124	—	4 (19%)	—	.071	—
1–5	35	4 (11%)	22 (63%)	6 (17%)	.138	6 (17%)	15 (43%)	4 (11%)	.079	—
6–10	21	1 (5%)	8 (38%)	4 (19%)	.139	1 (5%)	8 (38%)	—	.086	2 (9%)
11–15	13	—	5 (38%)	—	.152	1 (8%)	5 (38%)	—	.089	—
16–20	8	1 (12%)	4 (50%)	1 (12%)	.153	1 (12%)	2 (25%)	—	.085	—
21–30	5	—	—	—	.166	—	1 (20%)	—	.093	—
31–40	7	—	2 (28%)	—	.152	—	3 (42%)	—	.087	—
Totals	110	7 (6%)	55 (50%)	15 (14%)		9 (8%)	38 (34%)	4 (3%)		2 (2%)

*An intrinsicoid deflection in Lead V_1 of over 0.032 sec. in children (to 15 years of age), and over 0.04 sec. in adults was considered delayed.

†An intrinsicoid deflection in Lead V_6 of over 0.04 sec. in children, and over 0.06 in adults was considered delayed.

‡RSR′, RSr′, and rSRS are included together as examples of hypertrophy of the crista supraventricularis.

§R, qR, and Rs patterns are included together as examples of generalized hypertrophy of the right ventricle.

¶The R/S ratio in Lead V_1 was considered to be abnormally large when it was 4 or greater in children up to 5 years of age. Beyond 5 years of age a ratio of unity or greater was abnormal.[23]

higher than normal. These authors stated that there was no significant relationship between hemodynamic and electrocardiographic data in ventricular septal defect. Toscano-Barboza and DuShane[15] examined the electrocardiograms of 60 patients with ventricular septal defect in whom the anatomic location of the defect was recognized at surgery. Patients with defects of the inflow tract tended to have electrocardiographic manifestations in Lead V_1 (RSR′) which were considered indicative of diastolic overloading of the right ventricle, and patients with defects of the outflow tract had manifestations in Lead V_1 (qR) which were considered indicative of systolic overloading.

Most investigators agree that when the right ventricular pressure is normal, as in the maladie de Roger, the ECG is normal.

The ventricular gradient ($\hat{G}$) in ventricular septal defect has not been investigated, and the spatial vectorcardiogram (sVCG) in this malformation has received little attention. Braunwald and associates[17] studied the vectorcardiograms in 12 patients with ventricular septal defect and found what they considered to be a normal balance of electrical forces in 10 of these patients. They were of the opinion that in ventricular septal defect the work of both ventricles was increased and the normal vectorcardiogram merely indicated that the normal balance of electrical forces was maintained.

This report is concerned with the electrocardiograms and ventricular gradients of 110 patients with uncomplicated ventricular septal defect, and the spatial vectorcardiograms of 25 of these patients. Certain electrocardiographic and hemodynamic correlations were also obtained.

TO AGE IN 110 PATIENTS WITH ISOLATED VENTRICULAR SEPTAL DEFECT

RSR' PATTERN IN LEAD V_1‡	R PATTERN IN LEAD V_1§	MEAN R/S LEAD V_1	MEAN R/S LEAD V_6	ABNORMAL R/S RATIO IN LEAD V_1¶	MYOCARDIAL DISEASE (T-WAVE ABNORMALITY)	ABNORMAL VENTRICULAR GRADIENT	Q WAVE IN LEAD V_6 > 2 MV.	KATZ-WACHTEL PHENOMENON	MEAN RV SYSTOLIC PRESSURE (MM. Hg)	SHUNT MEAN PBF / SBF	COMPLETE RBBB
5 (24%)	12 (57%)	1.7	2.7	3 (14%)	4 (19%)	13 (33%)	6 (28%)	12 (57%)	55	2.4	—
10 (35%)	20 (57%)	4.0	4.5	9 (26%)	5 (14%)	18 (51%)	15 (43%)	14 (40%)	63	1.8	—
6 (28%)	9 (43%)	4.3	3.8	12 (57%)	3 (14%)	12 (52%)	8 (38%)	12 (57%)	63	1.9	2 (9%)
8 (61%)	3 (23%)	3.5	4.9	7 (54%)	2 (15%)	5 (23%)	5 (38%)	5 (38%)	49	1.2	—
3 (37%)	3 (37%)	4.2	4.8	3 (37%)	1 (13%)	1 (13%)	2 (25%)	1 (13%)	64	0.9	—
1 (20%)	—	0.2	19.3	—	2 (40%)	2 (40%)	2 (40%)	—	40	1.1	—
2 (28%)	—	0.4	7.5	1 (14%)	3 (43%)	3 (43%)	1 (14%)	—	37	1.7	—
36 (33%)	47 (42%)			35 (32%)	20 (18%)	54 (49%)	39 (35%)	44 (43%)			2 (2%)

MATERIALS AND METHODS

The electrocardiograms of 110 patients with uncomplicated ventricular septal defects and the spatial vectorcardiograms of 25 of these patients were studied. The patients were from the Charity Hospital of Louisiana in New Orleans.

The presence of the defect was diagnosed by cardiac catheterization in all of the patients. Additional proof was obtained at surgery in 12 instances and at autopsy in 11 instances. All of the patients had an increase in oxygen content at the right ventricular level of at least 1.0 volume per cent, as compared to the oxygen content of a right atrial sample. Patients who had a pressure gradient of more than 20 mm. Hg between the right ventricular cavity and the main pulmonary artery, or in whom associated defects were identified, were excluded from this study.

The sVCG was recorded using the equilateral tetrahedral reference system, as previously described from this laboratory.[18] The ventricular gradient was obtained by methods previously presented,[19,20] except that the electrocardiograms were projected and enlarged four times with an epidiascope for analysis.

The patients ranged in age from 2 months to 39 years; the mean age was 9.3 years. Fifty-three were males and 57 were females; 66 were white and 44 were Negro. The age distribution of the patients is shown in Table I.

RESULTS

The Electrocardiogram.—The electrocardiographic manifestations in the 110 patients with ventricular septal defect are summarized in Tables I and II, and in Figs. 1 and 2.

The atrial complex (P wave): The P-R interval was prolonged in 9 patients (8 per cent). There was little electrocardiographic evidence of atrial enlargement. An abnormally large P wave was found in Leads II or III in only 15 patients (14 per cent), and a P wave of the type associated with mitral stenosis was present in Lead I in 2 patients (2 per cent). A definite Q wave in the precordial leads to the right of the transition zone, considered by some[21] to indicate right atrial enlargement, was present in 7 (6 per cent) of the patients studied. Atrial fibrillation was present in 2 patients.

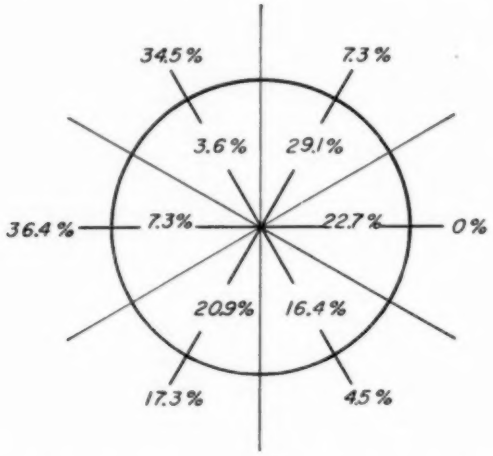

Fig. 1.—The six values within the circle represent the percentage distribution of the positions of the early vectors of ventricular activation in the frontal plane in the triaxial reference system, determined from the QRS complex of the standard leads of the ECG, for the 110 patients studied. The values outside the circle are for late vectors of ventricular activation. The late phases of depolarization for over 85 per cent of the patients were directed to the right in the frontal plane projection.

TABLE II. DISTRIBUTION OF THE MAGNITUDE OF THE Q WAVE IN LEAD V_6 ACCORDING TO NUMBER OF PATIENTS

MILLIVOLTS	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10
Number of Patients	1	9	10	8	5	2	1	3

The ventricular complex (QRS): In general, there were prominent S waves in Leads I, II, V_5, and V_6, prominent Q waves in Leads V_5 and V_6, and an R′ wave in Lead V_1 (rR′ or RSR′). Occasionally, the S waves in Leads V_5 and V_6 were wide enough to prompt such interpretations as "delayed right bundle branch conduction" or "incomplete right bundle branch block," as described previously for hypertrophy of the crista supraventricularis.[22] In most instances, however, the S wave tended to be prominent but not wide.

The early mean instantaneous vectors of ventricular activation were directed to the left, and the late mean vectors were directed to the right in the frontal plane (Fig. 1). This tendency for the late vectors of ventricular activation to be oriented to the right resulted in an S_1, S_2, S_3 pattern in 35 per cent of the patients and in an S_1S_2 pattern in 36 per cent of the patients.

An important electrocardiographic manifestation in this defect was the prominent Q wave in Lead V_6, which was greater than 2 mv. in magnitude for 39 (35 per cent) of the patients (Table I). The great magnitude that the Q wave in Lead V_6 occasionally reached is shown in Table II.

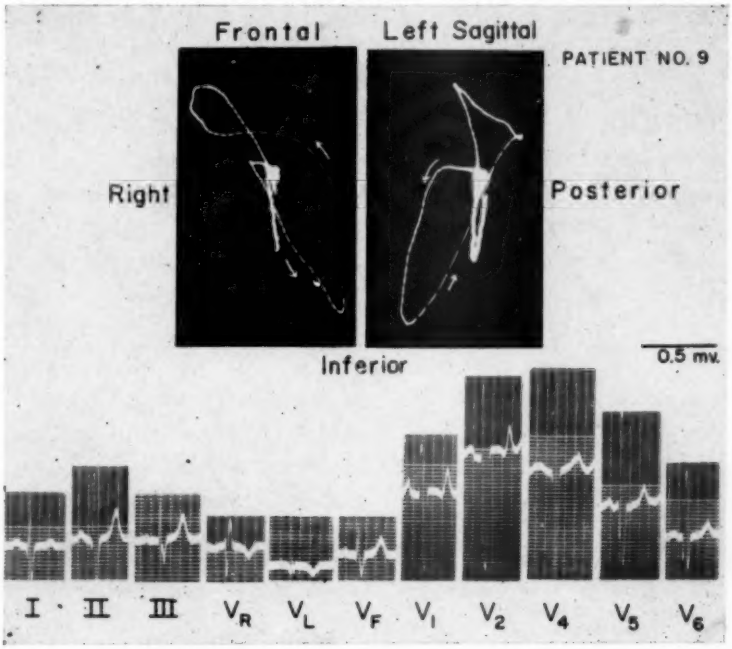

Fig. 2.—A typical sVCG and ECG of isolated ventricular septal defect. These types of tracings were characteristic of the patients whose electrocardiograms displayed the $S_1S_2S_3$ pattern. Consult text for details.

There was a tendency for the R and/or R′ wave in Lead V_1 to be of large magnitude with respect to the S wave in Lead V_1 (Table I). The incidence of right ventricular hypertrophy, when the criteria of Sokolow and Lyon[23] are used, was 32 per cent. However, these criteria for RVH are inadequate when hypertrophy of the crista supraventricularis exists without generalized RVH. The incidence of hypertrophy of the crista supraventricularis (RSR′) without generalized RVH (R/S normal) was 33 per cent. Electrocardiographic evidence of right ventricular hypertrophy and/or hypertrophy of the crista supraventricularis was present in 65 per cent of the patients studied. Electrocardiographic manifestations of combined right and left ventricular hypertrophy were present in 23 per cent of the patients, whereas electrocardiographic manifestations of isolated left ventricular hypertrophy were present in only 2 per cent of the

patients. In 9 per cent of the patients the ECG failed to display evidence of either right or left ventricular hypertrophy.

The *duration* of the QRS interval was normal in all but 2 of the patients. Both of these patients had right bundle branch block (RBBB). The intrinsicoid deflection was delayed in Lead V_1 in 38 (34 per cent) of the patients.

The repolarization complex (T wave): The T wave was considered to be abnormal and indicative of myocardial disease in 20 (18 per cent) of the 110 patients.

Comment: The determination of right and left ventricular hypertrophy in ventricular septal defect has been based upon criteria and experience gained primarily from the study of adults. There has been little effort to define right and left ventricular hypertrophy by measurement of the muscle masses of the right and left ventricles separately. Measurements of muscle thickness can be misleading, especially in the presence of ventricular dilatation. It is possible

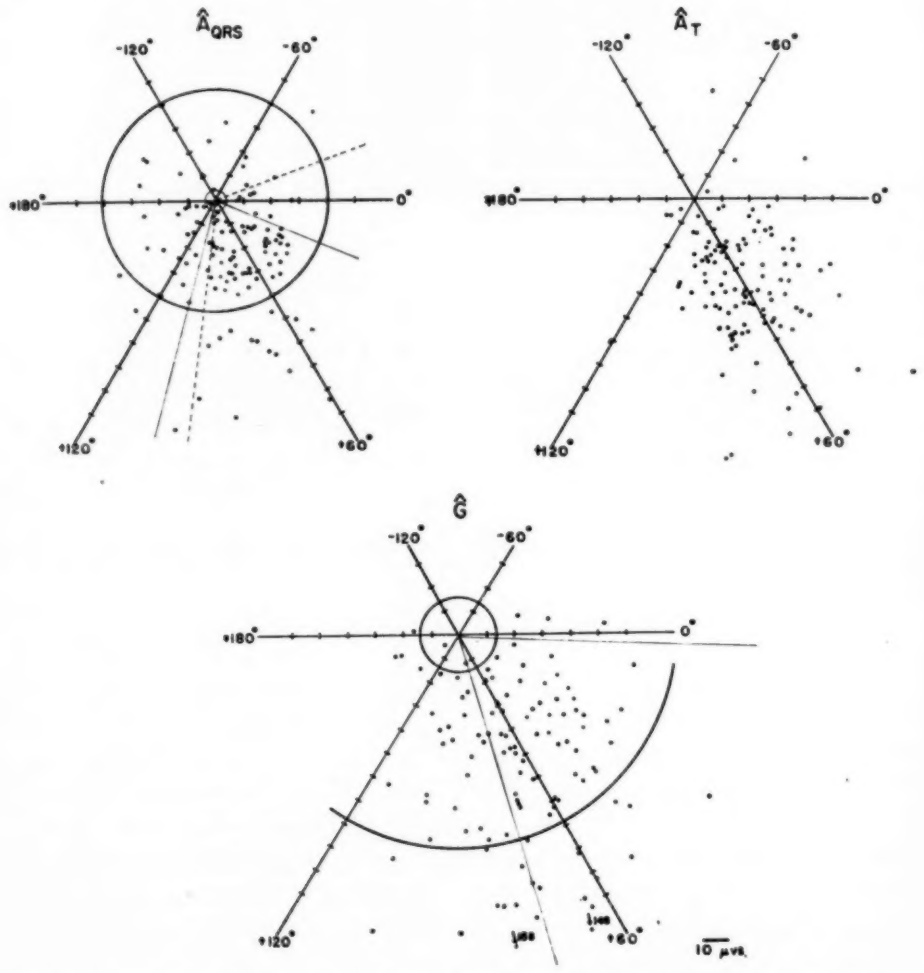

Fig. 3.—Magnitude and direction of $\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ for 110 patients with isolated ventricular septal defect. The circles represent the extreme values for the normal magnitude of $\hat{A}_{QRS}$ and $\hat{G}$, and the straight lines the extreme values for normal direction in the adult (solid line) and child (broken line).

that the large Q waves in Leads V_5 and V_6 reflect hypertrophy of the septal portion of the left ventricle, but this relationship has not been definitely established and needs careful study, particularly with autopsy correlation.

It appears, however, that RVH, including hypertrophy of the crista supraventricularis, is common in ventricular septal defect, whereas LVH is relatively uncommon. The narrow Q wave of large magnitude in Leads V_5 and V_6, the narrow S wave of large magnitude in the standard leads and in Leads V_5 and V_6, and the R′ wave in Lead V_1 are fairly characteristic of ventricular septal defect. These electrocardiographic manifestations are easily understood if it is remembered that the process of ventricular depolarization in normal hearts usually terminates in the base of the left ventricle. This results in a vector which is usually directed to the left in the frontal plane projection and oriented between 0° and −90°. Such a vector would result in the formation of an S wave in Lead III or in Leads II and III, depending upon whether it is located to the left or right of the −30° axis. If there is hypertrophy of the crista supraventricularis, for example, in association with intracardiac left-to-right shunts, the process of ventricular depolarization may no longer terminate in the base of the left ventricle, but rather in the posterior basal portion of the right ventricle. The crista supraventricularis hypertrophies when an increased volume of blood is pumped by the right ventricle. The vector produced by activation of the crista supraventricularis is usually directed to the right of the −90° axis of the frontal plane (Fig. 1). When this vector lies between −90° and −150°, an S wave is found in the three standard limb leads (S_1,S_2,S_3 pattern). The S_1,S_2,S_3 pattern was present in 35 per cent of the 110 patients. If the "cristal vector" is located between −150° and +150°, an S wave is formed in Leads I and II only (S_1,S_2 pattern).

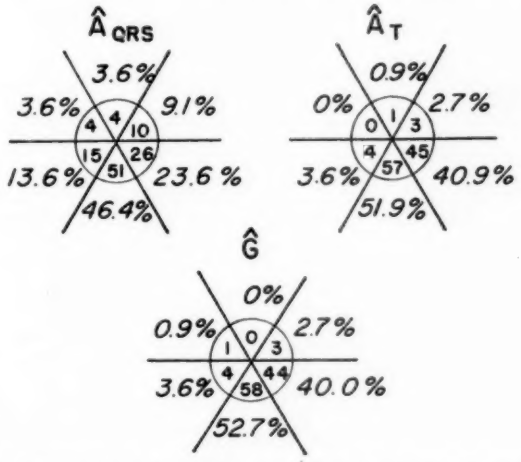

Fig. 4.—Variations in direction of $\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ in the frontal plane projection according to the number of patients (values inside the circle) and percentage of the total number of patients (values outside the circle).

The S_1,S_2 pattern was present in 36 per cent of the patients of this series. The rightward direction of the late vectors of ventricular depolarization in the frontal plane projection occurred in 88 per cent of the 110 patients. A typical ECG and sVCG of a patient with ventricular septal defect can be seen in Fig. 2.

TABLE III. VARIATIONS IN $\hat{A}_{QRS}$, $\hat{A}_T$, AND $\hat{G}$ WITH AGE, IN THE 110 PATIENTS WITH CONGENITAL VENTRICULAR SEPTAL DEFECT

AGE GROUP	NUMBER OF PATIENTS	$\hat{A}_{QRS}$		$\hat{A}_T$		$\hat{G}$		$\hat{G}$:$\hat{A}_{QRS}$ MEAN
		MEAN POSITION (DEGREES)	MEAN MAGNITUDE (μV.S.)	MEAN POSITION (DEGREES)	MEAN MAGNITUDE (μV.S.)	MEAN POSITION (DEGREES)	MEAN MAGNITUDE (μV.S.)	
0–1	21	76	27.0	70	31.0	72	49.1	2.2
1–5	35	73	27.8	60	39.5	67	59.6	2.6
6–10	21	109	24.9	65	45.2	79	62.8	3.2
11–15	13	59	26.8	46	37.2	63	58.6	4.2
16–20	8	64	22.5	35	41.5	54	54.5	2.6
21–30	5	57	31.0	50	42.5	56	73.7	2.4
31–40	7	31	33.0	58	49.7	39	84.2	2.6
Mean		75	26.7	59	38.8	67	63.2	2.7

TABLE IV. RELATIONSHIP OF $\hat{G}$ TO $\hat{A}_{QRS}$ AND TO $\hat{A}_T$ IN THE FRONTAL PLANE PROJECTION

POSITION OF $\hat{A}_{QRS}$ RELATIVE TO $\hat{G}$	NUMBER OF PATIENTS	$\hat{A}_{QRS}$—$\hat{G}$			POSITION OF $\hat{A}_T$ RELATIVE TO $\hat{G}$	NUMBER OF PATIENTS	$\hat{G}$—$\hat{A}_T$		
		0°–35°	36°–70°	>70°			0°–35°	36°–70°	>70°
Right	73	49	15	9	Right	37	33	3	1
Left	37	18	16	3	Left	73	62	7	4

In addition to the S waves in the standard leads, the "cristal vector," which is directed spatially toward the right shoulder, would produce late S waves in the precordial leads recorded from the left of the transition zone as terminal R′ waves in Leads V_1 and V_2.

In some normal individuals the posterobasal region of the right ventricle is the last portion of the ventricular musculature to be depolarized. This results in late vectors which are directed upward and toward the right. In such a situation it is difficult, and sometimes impossible, to differentiate hypertrophy of the crista supraventricularis from normal ventricular depolarization terminating in the base of the right ventricle. However, if hypertrophy of the crista supraventricularis is present, the terminal vector is exaggerated in duration and magnitude. The deep S waves in Leads V_5 and V_6, the late prominent R′ wave in Lead V_1, and the terminal appendage seen in the sVCG are not normal events. Instead, they are manifestations of hypertrophy in the region of the heart which is last to be activated.

It seems, therefore, that the electrocardiographic manifestations of ventricular septal defect are primarily those of hypertrophy of the crista supraventricularis, which includes an S_1,S_2,S_3 or S_1,S_2 pattern in the standard leads, S waves in the unipolar precordial leads recorded from the left of the transition zone, and terminal R′ waves in Leads V_1 and V_2.

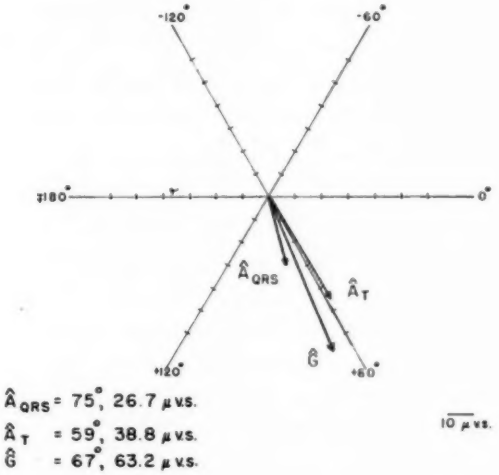

Fig. 5.—Mean $\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ for the 110 patients with congenital ventricular septal defect.

The Ventricular Gradient.—The magnitude and direction of $\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ for the patients with ventricular septal defect are summarized by Tables III and IV and Figs. 3, 4, and 5. There was considerable variation in the magnitude and direction of $\hat{A}_{QRS}$. The majority of the vectors were directed to the left and inferiorly in the frontal plane projection (Figs. 3 and 4). The mean direction of $\hat{A}_{QRS}$ was 75°, and the mean magnitude was 26.7 μv.s. (Table III; Fig. 5). The projection of $\hat{A}_T$ in the frontal plane was rather consistently directed to the left and inferiorly (Figs. 3 and 4), with a mean direction and magnitude of 59° and 38.8 μv.s., respectively (Table III; Fig. 5). The $\hat{G}$ in the frontal plane

projection had a mean direction of 67° and a mean magnitude of 63.2 μv.s. (Table III; Fig. 5). The average ratio of $\hat{G}$:$\hat{A}_{QRS}$ was 2.7, a value which is considered to be normal.[24]

Comment: The ventricular gradient, an expression of the variations in duration of the excited state,[25] should be of considerable importance in the study of congenital heart disease whenever myocardial hypertrophy can obscure the electrophysiologic state of the myocardium. Of the patients considered in this study, only 20 (18 per cent) had T waves which were interpreted as indicating myocardial disease, whereas the ventricular gradient was abnormal in 54 (49 per cent) of the patients. The ventricular gradient was considered to be abnormal for any one of the following reasons: (a) direction (normal, 2.2° to 72.2°); (b) magnitude (normal, 13.5 to 78.9 μv.s.); (c) angular relationship to $\hat{A}_{QRS}$ (normal, <30°).[24,26] These data indicate that the time course of the duration of the excited state was abnormal in about half of the patients with ventricular septal defect.

The $\hat{A}_{QRS}$ (corrected for age) was deviated to the right beyond the normal in 30 patients (27 per cent). This was particularly true when the right ventricular systolic pressure was high (Fig. 6).

Spatial Vectorcardiogram.—The spatial vectorcardiographic findings for 25 patients with ventricular septal defect are summarized by Table V and Figs. 2, 7, 8, 9, and 10. The maximal instantaneous vectors of the QRSsÊ and TsÊ loops were directed inferiorly to the left and slightly anteriorly (Fig. 7). The mean values of the maximal instantaneous QRS and T vectors for the frontal and left sagittal plane projections are shown in Table V. The range in spatial orientation of the QRSsÊ loop was greater than that of the TsÊ loop.

Comment: In general, the configuration and spatial orientation of the QRSsÊ loop which are most diagnostic of ventricular septal defect are shown in Fig. 2. The QRSsÊ loop is characterized by counterclockwise rotation in the frontal plane projection and a fairly prominent terminal portion which is posterior and superior to the isopotential point. This late portion of the QRSsÊ loop was also usually oriented to the left of the isopotential point. In many respects this configuration resembled an exaggerated Type-2 normal pattern previously described.[18] The terminal portion of the QRSsÊ loop occasionally was inscribed slowly, but this was not consistently true. A typical ECG and sVCG of ventricular septal defect are shown in Fig. 2. The electrocardiographic tracing shows the prominent Q waves in Leads I, V_5, and V_6, and prominent S waves in all of the standard leads and in Leads V_5 and V_6. By inspection of the sVCG it can be seen that the late vectors of ventricular activation are oriented to the left of −150°, thus the S_1,S_2,S_3 pattern displayed in the standard limb leads.

The TsÊ loop was usually oriented to the left and inferior to the isopotential point (Fig. 2). Fig. 7 summarizes the spatial orientation of the TsÊ loops.

There were some deviations from the typical pattern of the sVCG described for ventricular septal defect. For example, Fig. 8 shows the sVCG of a patient with a very small ventricular septal defect (maladie de Roger) and insignificant shunting of blood. Except for slight distortion of the QRSsÊ loop, the sVCG and ECG were normal.

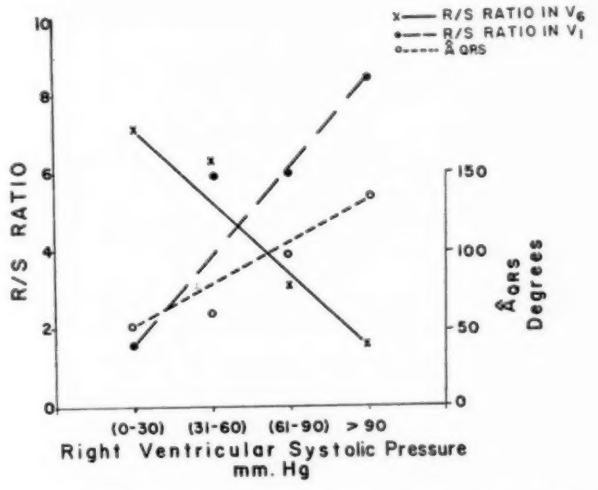

Fig 6.—Relationship of the R:S ratio in Lead V_6, R:S ratio in Lead V_1, and direction of $\hat{A}_{QRS}$ in the frontal plane projection to right ventricular systolic pressure.

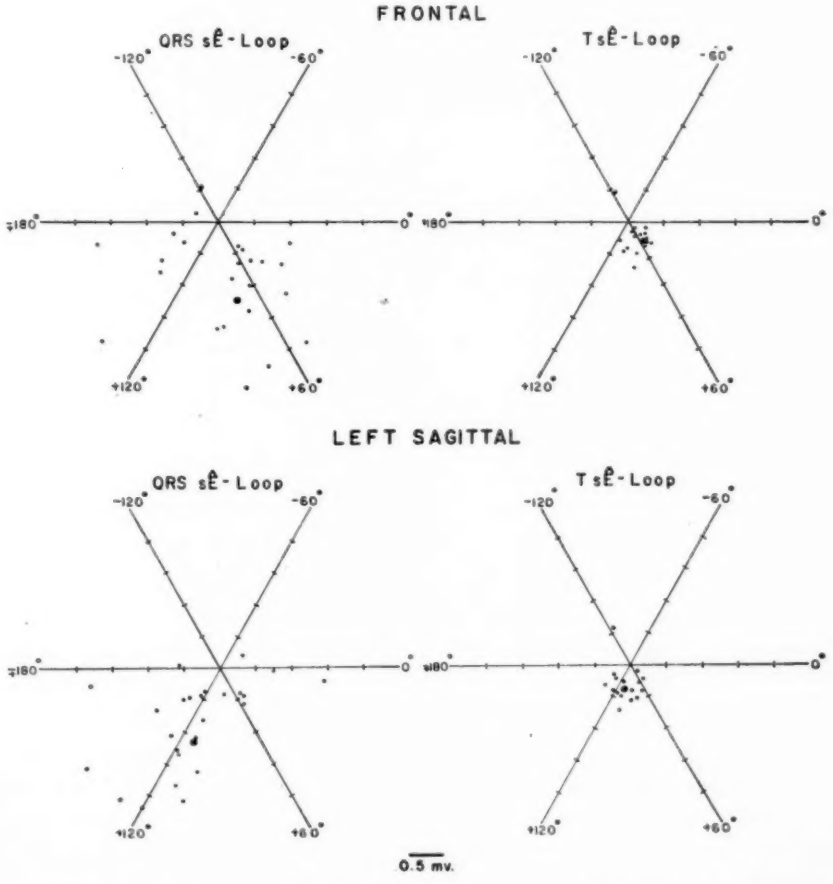

Fig. 7.—Magnitude and direction of the maximal instantaneous vectors of the QRSsÊ and TsÊ loops in the frontal and left sagittal plane projections for 25 patients with isolated ventricular septal defect.

TABLE V. VARIATIONS IN DIRECTION AND MAGNITUDE OF THE MAXIMAL INSTANTANEOUS VECTORS OF THE QRSsÊ AND TsÊ LOOPS OF 25 PATIENTS WITH CONGENITAL ISOLATED VENTRICULAR SEPTAL DEFECT

	MAXIMAL VECTORS IN FRONTAL PLANE				MAXIMAL VECTORS IN SAGITTAL PLANE			
	QRSsÊ LOOP		TsÊ LOOP		QRSsÊ LOOP		TsÊ LOOP	
	DIRECTION (DEGREE)	MAGNITUDE (MV.)	DIRECTION (DEGREE)	MAGNITUDE (MV.)	DIRECTION (DEGREE)	MAGNITUDE (MV.)	DIRECTION (DEGREE)	MAGNITUDE (MV.)
Minimal	−118	0.34	−117	0.12	− 28	0.36	50	0.11
Maximal	198*	2.30	117	0.63	184	2.30	243	0.61
Average	76	1.10	52	0.34	102	1.08	107	0.38

*For convenience, when the vector rotated in a clockwise direction beyond 180°, it was assigned a positive value; in this instance, +198° rather than −162°.

Fig. 9 shows an sVCG in which there is relatively long duration of the late phases of ventricular depolarization. The sVCG and the ECG resemble "incomplete right bundle branch block" or "delayed conduction in the right bundle," such as was discussed for atrial septal defect.[22] Such configurations are probably the result of hypertrophy of the crista supraventricularis and not right bundle branch block.[22,27,28] The early and middle portions of the QRSsÊ loop are oriented superiorly and to the left of the isopotential point, whereas the late portions of the QRSsÊ loop are oriented superiorly and between −90° and −150° in the frontal plane, resulting in the S_1,S_2,S_3 pattern. In addition to hypertrophy of the crista supraventricularis, early left ventricular hypertrophy was present. As stated above, the typical ECG pattern of isolated LVH was rare in the 110 patients studied.

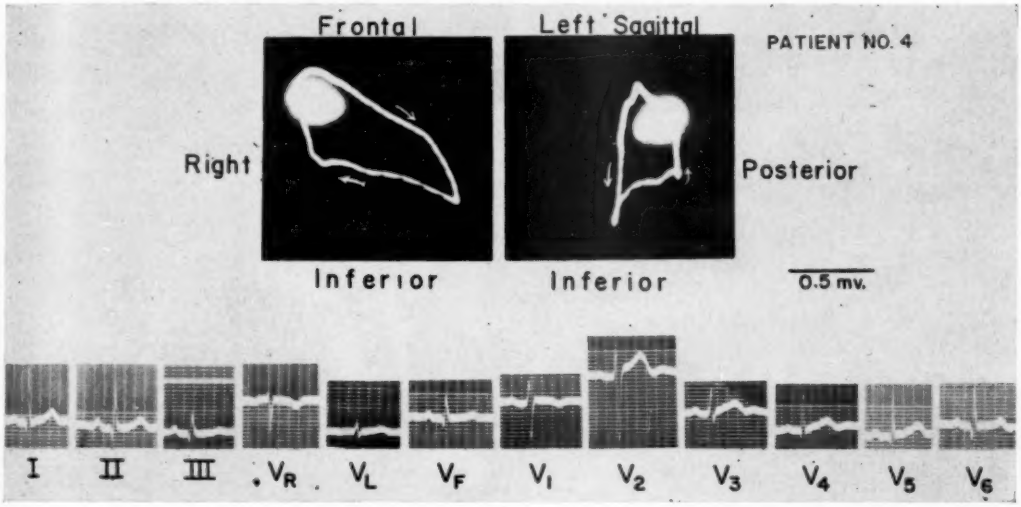

Fig. 8.—sVCG and ECG of a patient with a small ventricular septal defect (maladie de Roger).

Fig. 10 shows the type of sVCG encountered when marked right ventricular hypertrophy was present. The QRSsÊ loop was oriented inferiorly, anteriorly, and to the right of the isopotential point. This type of loop was found in 3 of the 25 patients in whom the sVCG was recorded.

There were small variations in spatial orientation of the TsÊ loop, but, as a whole, it tended to conform to the normal pattern.[18] The junction (J) of the QRSsÊ and TsÊ loops and the S-T segment were not displaced.

In general, the QRSsÊ and TsÊ loops tended to be smooth in outline. In only one instance did the QRSsÊ loop show marked distortion such as has been described for multiple myocardial infarctions or diffuse myocardial disease.

The Electrocardiographic and Hemodynamic Correlations.—Hemodynamic and electrocardiographic correlations in congenital cardiac defects, for the most part, have been disappointing. As stated previously,[22] the brief moment of sampling at cardiac catheterization probably does not represent the true hemodynamic status of the patient any more than does a single recording of systemic arterial

blood pressure. Nevertheless, certain trends were found, such as an increase of the R/S ratio in Lead V_1 with increasing right ventricular systolic pressure in pulmonary stenosis,[29,30] and a shift of the $\hat{A}_{QRS}$ and the QRSsÊ loop to the left in ostium primum defects and to the right in ostium secundum defects.[22,31]

In the 110 patients with ventricular septal defect studied in this investigation, there was a tendency for the R/S ratio to increase in Lead V_1 and to decrease in Lead V_6 with elevation of right ventricular systolic pressure. Also, the $\hat{A}_{QRS}$ tended to shift more to the right in the frontal plane with higher right ventricular pressures (Fig. 6).

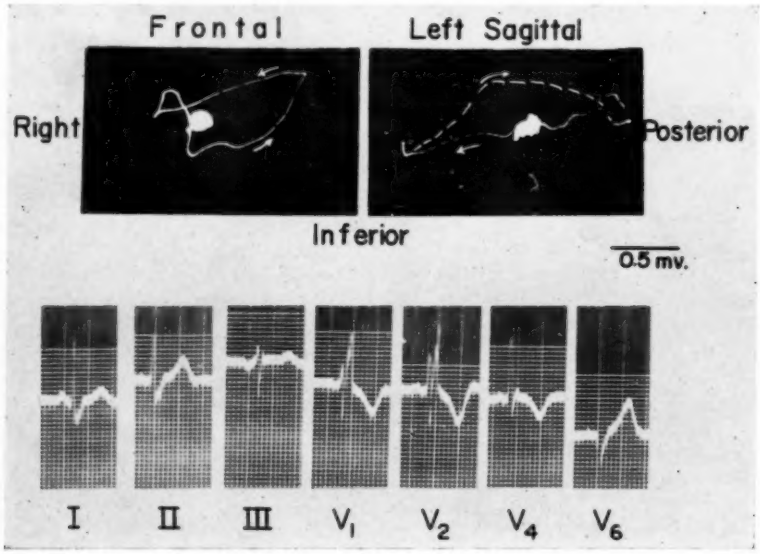

Fig. 9.—sVCG and ECG of a patient with a large ventricular septal defect with so-called "incomplete right bundle branch block," due primarily, if not only, to hypertrophy of the crista supraventricularis. Consult text for details.

GENERAL DISCUSSION

The electrocardiogram and spatial vectorcardiogram in uncomplicated ventricular septal defect were fairly characteristic. An S_1,S_2,S_3 or S_1,S_2 pattern in the standard leads, an R′ wave in Lead V_1, S waves of large magnitude in in Leads V_5 and V_6, a deep Q wave in Lead V_6, and a QRSsÊ loop of the sVCG in which the late vectors of ventricular activation are prolonged and oriented superiorly and to the right of the isopotential point seem to make up the characteristic pattern for the patients studied. The combination of these findings in the ECG and sVCG of a patient with clinical data suggestive of ventricular septal defect was found to be of value in diagnosis in approximately 80 per cent of the patients. Surprisingly, the electrocardiographic pattern of isolated LVH was uncommon. Unfortunately, the medical literature contains little quantitative information on the ECG and sVCG in right or left ventricular hypertrophy in infants and children. Ventricular muscle mass has not been adequately studied in ventricular septal defect, so that the actual incidence of RVH or LVH and

the relationship of hypertrophy to the ECG or sVCG is not known. Measurement of muscle thickness is a poor index of ventricular hypertrophy, but even this measurement has been neglected.

Most studies in which anatomic and electrocardiographic correlations have been attempted have been based upon estimation of chamber size from roentgenograms or at surgery, both of which are unreliable. However, if electrocardiographic and vectorcardiographic criteria developed for adults are utilized, it appears that LVH alone (2 per cent) or in combination with RVH (23 per cent) was uncommon among the 110 patients studied. A large number of patients manifested hypertrophy of the crista supraventricularis (33 per cent). These differences may be due to the anatomic location of the defect; for example, those defects in the membranous portion of the septum tend to display patterns consistent with generalized RVH in Lead V_1 (qR, R), and those defects in the muscular portion of the septum display electrocardiographic manifestations of hypertrophy of the crista supraventricularis (RSR′).[15] However, this problem must remain unsolved until more extensive correlations of the ECG and sVCG with autopsy data are obtained.

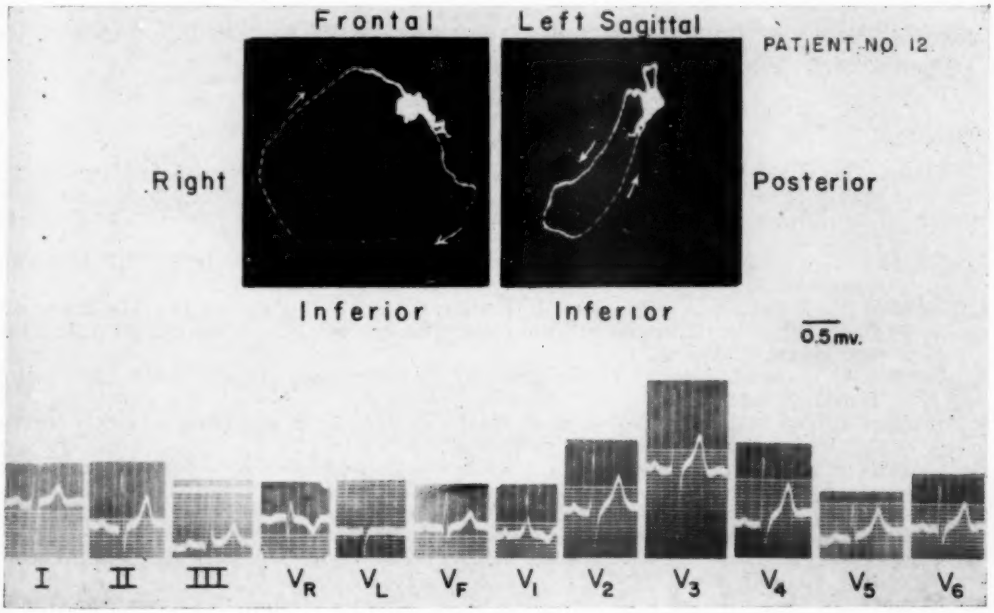

Fig. 10.—sVCG and ECG of a patient with a large ventricular septal defect and electrocardiographic and vectorcardiographic evidence of RVH. Note that the QRSsÊ loop is distorted very little.

The ECG and sVCG indicated little myocardial degeneration. In only 18 per cent of the patients were there T-wave abnormalities such as are seen with myocardial disease, and the QRSsÊ loop was not significantly distorted or narrowed. In Fig. 10 the ECG and sVCG show marked RVH, but the QRSsÊ loop is smooth and the TsÊ loop is normal, as are the T waves in the ECG. This patient had an abnormal ventricular gradient. The electrical manifestations were

due apparently to alterations in spatial orientation of the muscle masses. Forty-nine per cent of the patients studied had abnormal ventricular gradients. In a previous study of 100 patients with atrial septal defects,[22] only 16 per cent of the patients had T-wave abnormalities, whereas the $\hat{G}$ was abnormal in 44 per cent of those patients. If more can be learned about the ventricular gradient in congenital heart disease, it may eventually be possible to distinguish patients with hypertrophy and myocardial disease from patients with hypertrophy alone.

SUMMARY

The ECG, sVCG, and $\hat{G}$ were studied in 110 patients with isolated ventricular septal defect. The electrocardiographic pattern consisted of an S_1,S_2,S_3 pattern in the standard leads, a qR or RSR′ pattern in Lead V_1, deep S waves in Leads V_4, V_5, and V_6, and a Q wave of large magnitude in Lead V_6. The sVCG characteristically displayed prolongation of the terminal vectors of ventricular activation. Isolated or combined LVH was relatively uncommon.

The ventricular gradient was abnormal in about half of the patients; T-wave abnormalities, however, were seen in only 18 per cent of the electrocardiograms. It is suggested that the ventricular gradient may be useful in distinguishing hypertrophy alone from hypertrophy associated with myocardial degeneration in patients with congenital heart disease.

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Transient Effect of Potassium on A-V Conduction and Ventricular Tachycardia Produced by Acetyl-Strophanthidin: Demonstration of Supernormal Conduction

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Earlier studies in man indicated that the elimination of ventricular premature systoles (VPS) accompanying atrial fibrillation by intravenous potassium was short lived and was usually paralleled by a transient depression of atrioventricular (A-V) conduction.[1,2] The purpose of the present study was to determine whether the brief effects of potassium on the A-V conduction and especially on ventricular arrhythmia could be reproduced in laboratory animals.

METHOD

Twenty-nine experiments were performed in 6 mongrel dogs which ranged in weight from 9 to 15 kilograms. The dogs were anesthetized with 30 mg. of sodium pentobarbital per kilogram of body weight, administered intraperitoneally. The entire experiment was monitored with an oscilloscope, and permanent recordings were made whenever advisable.

The arrhythmia was produced with acetyl-strophanthidin; 0.6 mg. of the drug was diluted with 9 c.c. of saline, and 1 c.c. (0.06 mg.) of the solution was injected intravenously every 30 seconds. Because the peak action of acetyl-strophanthidin may not become manifest for from 5 to 10 minutes after the drug is given, the administration was usually discontinued short of ventricular tachycardia. Allowing for this lag, we were able to produce the desired tachycardia, usually identifiable as ventricular in origin. On the other hand, continuous administration of the drug until ventricular tachycardia appeared was often followed by ventricular fibrillation and death of the animal. The amount of acetyl-strophanthidin required to reach the desired end point was quite constant for a given animal, with an occasional variation of .12 mg. from injection to injection. The average dose necessary to produce the desired end point for Dogs 33, 34, 35, 36, 37, and 38, was 0.83, 0.91, 1.07, 1.06, 1.16, 1.26 mg., respectively.

The potassium was injected in the form of isotonic (155 mEq./L.) solution of buffered potassium phosphate in distilled water. A calibrated flowmeter was used to assure a constant flow from experiment to experiment. The rate of flow as determined from the flowmeter was checked against the rate determined from the volume of solution used and the time required for its infusion. The rate of injection varied from 1.10 to 1.23 mEq. per minute.

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Frequent determinations of plasma potassium were made. The detailed information as to the amount of acetyl-strophanthidin used, the rate at which potassium was infused, and plasma levels of the cation for each experiment are presented in Table I.

Following the above-outlined methods of administration of acetyl-strophanthidin and potassium, four different procedures were carried out: *Study I.* Acetyl-strophanthidin was administered until the desired end point was reached and the duration of the arrhythmia was observed. *Study II.* Potassium was administered until A-V block was produced. The duration of the conduction disturbance after infusion was discontinued was recorded. *Study III.* Acetyl-strophanthidin was given to the end point and then followed by potassium until A-V block was reached. The duration of A-V block was determined. *Study IV.* Acetyl-strophanthidin was given until the arrhythmia appeared. The arrhythmia was abolished by potassium, and at that point the injection of potassium was terminated. The duration of sinoatrial rhythm and that of the recurrent arrhythmia were carefully determined.

All four studies were performed on Dogs 33, 34, 35, 36, and 37, and Studies I, II, and IV were carried out on Dog 38.

RESULTS

The arrhythmia following the administration of acetyl-strophanthidin (Study I) lasted 15 and 16 minutes in Dogs 33, and 19, 18, 8, 16, and 14 minutes in Dogs 34, 35, 36, 37, and 38, respectively.

The duration of A-V block produced by potassium in Studies II and III varied from 1.5 to 3 minutes (Fig. 1), and the plasma level at that point varied from 7.3 to 9.4 mEq./L., with an average of 8.7 mEq./L. The average amount of solution injected before block was produced in the two studies was 18.5 and 19.0 mEq., respectively.

The ventricular arrhythmia which was induced by acetyl-strophanthidin was abolished uniformly by potassium in amounts varying from 2.1 to 6.0 mEq., with an average of 3.9 mEq. (Study IV). However, within one-half to 2 minutes after the infusion was discontinued, the ventricular arrhythmia reappeared (Fig. 2). The plasma potassium at the time the arrhythmia was abolished varied from 5.9 to 6.9 mEq./L., with an average of 6.4 mEq./L. The level of potassium when the arrhythmia recurred varied from 5.3 to 5.7 mEq./L., with an average of 5.5 mEq./L. The control potassium in dogs submitted to this study (Study IV) varied from 3.5 to 3.9 mEq./L., with an average of 3.8 mEq./L.

The administration of isotonic solution of sodium phosphate in doses three times as large as potassium phosphate was without any demonstrable effect on the electrocardiogram.

COMMENT

The results of the experiments indicate that the depression by potassium of A-V conduction and the arrhythmia induced by acetyl-strophanthidin is transient in character. These findings are in complete agreement with earlier observations made in human beings.[1,2]

An interesting fact was the uniformity with which we were able to produce A-V block with persistence of prominent P waves, and the frequency with which the supernormal phase of A-V conduction was elicited (Fig. 1). The latter has, to our knowledge, not been observed in an intact mammalian heart, although

TABLE I

	EXPERIMENT	AMOUNT INJECTED		RATE OF FLOW OF K (MEQ./MIN.)	DURATION OF ARRHYTHMIA DUE TO AS (MIN.)	DURATION OF SINUS RHYTHM (MIN.)	DURATION OF A-V BLOCK (MIN.)	PLASMA K (MEQ./L.)			
		AS (MG.)	K (MEQ.)					CONTROL	AT S-A RHYTHM	ON RETURN OF ARRHYTHMIA	AT A-V BLOCK
Dog 33:											
AS* to arrhythmia (Study I)	94	.84	—	—	15	—	—	—	—	—	—
	115	.84	—	—	16	—	—	—	—	—	—
K† to A-V‡ block (Study II)	83	—	20.2	1.12	—	—	2.0	4.0	—	—	8.3
AS and K to A-V block (Study III)	79	.84	16.8	1.12	—	—	1.5	3.9	—	—	8.8
	81	.78	16.5	1.18	—	—	2	3.9	—	—	9.4
AS and K to S-A§ rhythm (Study IV)	117	.84	5.6	1.13	12	1.0	—	3.8	6.6	—	—
Dog 34:											
AS to arrhythmia (Study I)	100	1.02	—	—	19	—	—	—	—	—	—
K to A-V block (Study II)	92	—	23.2	1.16	—	—	1.5	3.8	—	—	8.6
AS and K to A-V block (Study III)	90	.84	15.0	1.25	—	—	1.5	4.3	—	—	7.3
AS and K to S-A rhythm (Study IV)	119	.96	6.0	1.23	10	1.0	—	3.8	6.9	5.6	—
	139	1.02	3.9	1.12	6	0.5	2.0	3.9	6.6	—	8.5
	140	1.02	4.5	1.08	6	1.0	—	3.8	6.1	5.4	9.0

Dog 35:													
AS to arrhythmia (Study I)	105	1.02	—	—	18	—	—	—	—	—	—	—	—
K to A-V block (Study II)	95	—	12.3	1.23	—	—	2	3.5	—	—	—	8.2	
AS and K to A-V block (Study III)	91	1.14	21.0	1.23	—	—	1.5	3.3	—	—	—	9.0	
	138	1.02	12.0	1.00	—	—	2.0	3.8	—	—	—	7.7	
AS and K to S-A rhythm (Study IV)	120	1.08	3.6	1.20	6	1.0	—	3.7	6.9	5.6	—	—	
	137	.96	2.1	1.05	5	2.0	—	4.0	6.9	5.7	8.6		
Dog 36:													
AS to arrhythmia (Study I)	99	1.02	—	—	8	—	—	—	—	—	—	—	
K to A-V block (Study II)	103	—	18.8	1.17	—	—	2	—	—	—	—	7.8	
AS and K to A-V block (Study III)	101	1.14	21.0	1.16	—	—	4	3.7	—	—	—	8.5	
AS and K to S-A rhythm (Study IV)	121	1.02	2.6	1.10	9	1.0	—	3.5	6.1	5.3	—		
Dog 37:													
AS to arrhythmia (Study I)	102	1.20	—	—	16	—	—	—	—	—	—	—	
K to A-V block (Study II)	113	—	18.0	1.20	—	—	3	3.5	—	—	—	8.2	
AS and K to A-V block (Study III)	122	1.14	19.5	1.18	—	—	1.5	—	—	—	—	—	
AS and K to S-A rhythm (Study IV)	118	1.14	5.4	1.16	10	1.0	—	3.9	5.8	5.3	—		
Dog 38:													
AS to arrhythmia (Study I)	110	1.20	—	—	14	—	—	—	—	—	—	—	
K to A-V block (Study II)	123	—	19.5	1.1	—	—	4	4.0	—	—	—	8.7	
AS and K to S-A rhythm (Study IV)	131	1.32	2.5	1.18	6	1.0	—	3.9	5.6	—	—	7.5	

*AS: Acetyl-strophanthidin (Lilly). †K: Potassium phosphate. ‡A-V: Atrioventricular. §S-A: Sinoatrial.

unquestionable clinical cases have been observed.[3,4] The supernormal phase of A-V conduction as seen in Fig. 1 is indicated by the paradoxical relationship of R-P to P-R. The shorter R-P intervals are followed by shorter P-R intervals, and longer R-P intervals by longer P-R intervals. The appearance of a shorter P-R interval after a preceding longer R-R interval strengthens the interpretation. The possibility that the pattern is due to nodal or ventricular bigeminy is unlikely. The latter is ruled out by normally appearing QRS complexes (except

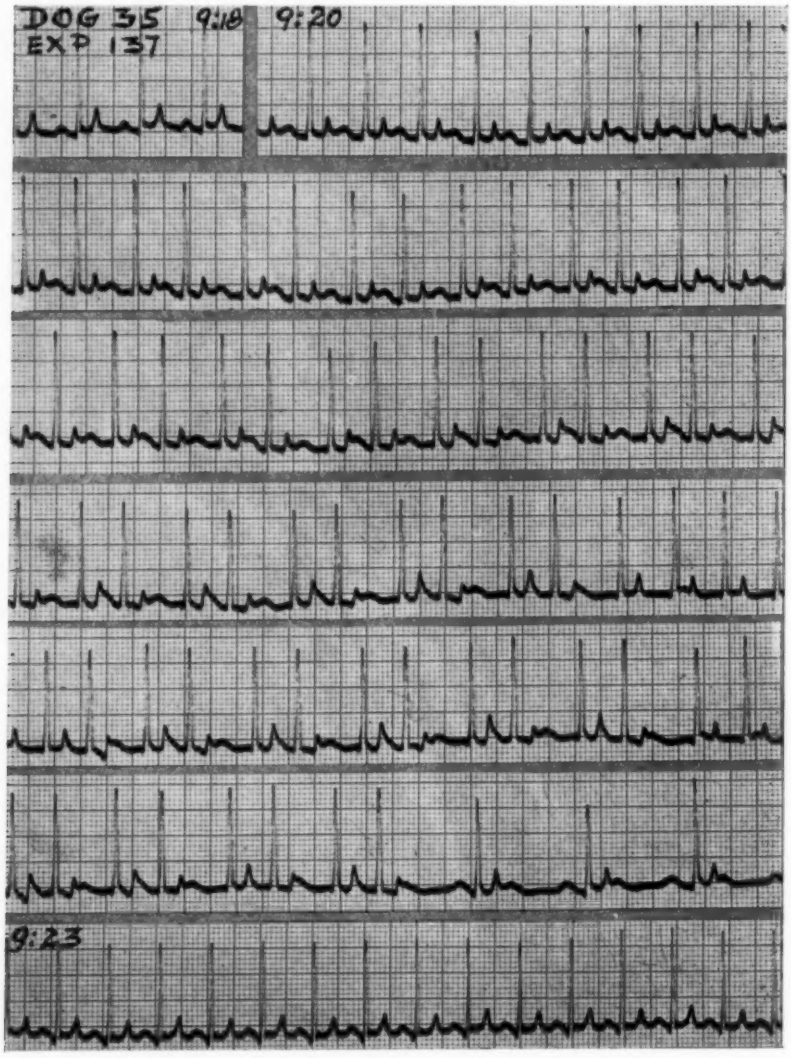

Fig. 1.—Dog 35, Experiment 137. This electrocardiogram (Lead II) demonstrates the transient effect of potassium on A-V conduction. The recording is continuous except for strips taken at 9:18 and 9:23. Infusion of potassium at a rate of 1.0 mEq./min. began at 9:09. The first evidence of disturbed A-V conduction appeared at 9:20 (row 1), manifest by prolonged P-R interval with gradual progression to second-degree heart block (row 6). At the moment the 2:1 block became manifest the infusion was discontinued; 3 minutes later (9:23 strip), sinus rhythm with normal P-R interval was present. The relation of R-P to P-R is paradoxical, in that shorter R-P are followed by shorter P-R and longer R-P by relatively longer P-R. Such a relationship indicates the existence of supernormal phase of A-V conduction.

when the R-R interval becomes quite short and aberrant ventricular conduction appears), and neither is likely in view of the fact that the R-R interval of the bigeminy becomes gradually shorter. Such a changing relationship would not be expected if the bigeminy were due to ordinary ectopic beats. Furthermore, it would be a most fortuitous coincidence to have the "ectopic" beats follow only the short R-P interval. It is not surprising that the "position" of the supernormal conduction in relation to the T wave, as represented by the P wave, seems to shift.

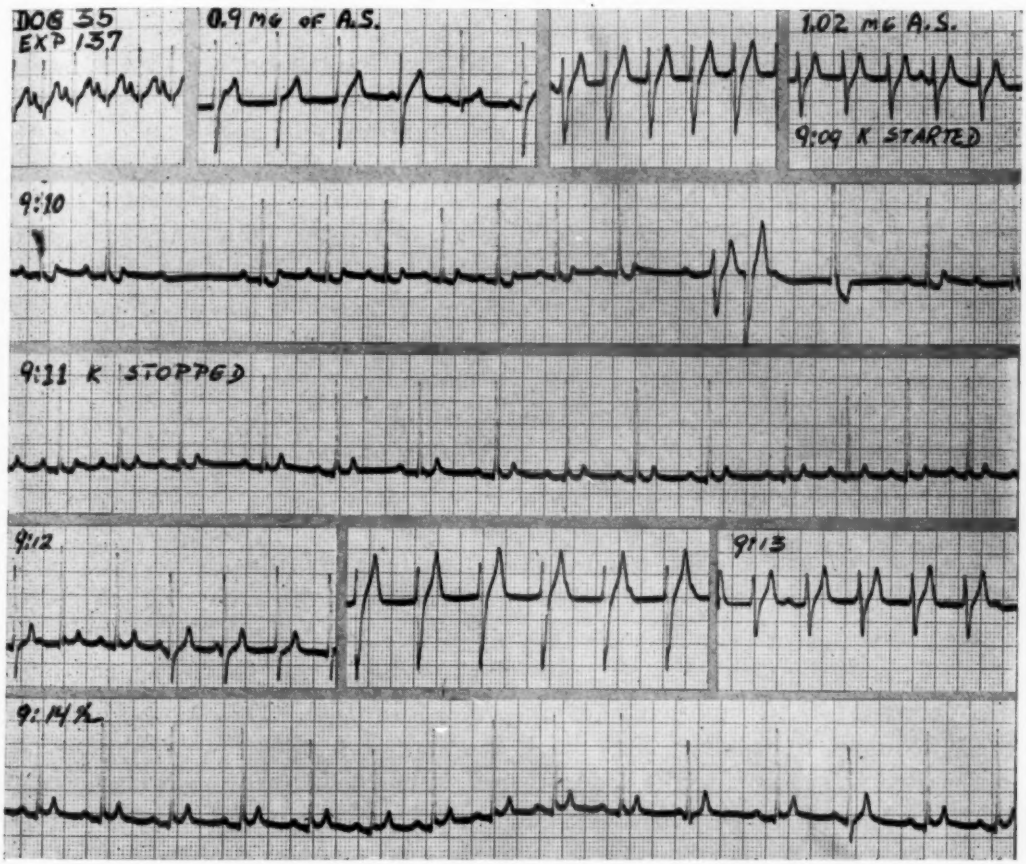

Fig. 2.—Dog 35, Experiment 137. This electrocardiogram (Lead II) is representative of the transient suppression of ventricular tachycardia by potassium. The tracing in the upper left corner is a control strip and demonstrates sinoatrial rhythm with a P-R interval of 0.10 second. Subsequent strips in row 1 show the development of ventricular tachycardia. At 9:09, an infusion of potassium was started at a rate of 1.0 mEq./min. After 3 minutes (9:10 strip), sinus rhythm appeared, but with persistence of a relatively longer P-R interval (0.16 to 20 second) and, at first, a second-degree heart block. At 9:11, infusion of potassium was stopped, and 1 minute later (9:12) the arrhythmia reappeared. Potassium was restarted at 9:13; at 9:14½, sinus rhythm was re-established and infusion was continued to A-V block (see Fig. 1). Note that the emergence of ventricular tachycardia, first as a direct result of acetyl-strophanthidin (row 1) and again upon discontinuation of potassium (row 4), was in both instances almost identical. At first the QRS complexes showed a deep S wave, with little increase in duration and with occasional conducted sinoatrial beats. Later the S waves became much deeper, the QRS wider, and the ventricular rate faster, with an easily identifiable slower sinoatrial rhythm. The possibility still remains that the arrhythmia represents nodal tachycardia with aberrant conduction and retrograde block. However, definite fusion (combination) beats present in other tracings support the diagnosis of ventricular tachycardia.

The supernormal phase may be truly shifting as a result of changing levels of plasma potassium. On the other hand, the P-R interval may be a poor index of its actual position in relation to the recovery curve of the A-V junction.

The A-V block due to potassium can be explained on the basis of elevation of plasma level of the cation. As the plasma potassium dropped because of an intracellular shift of the cation and/or diffusion into extravascular extracellular space, the conduction again became normal. It is quite possible that the shift into the myocardial cells was equally as great and as rapid as the shift into other cellular and extracellular compartments. If this were the case, then the restitution of normal A-V conduction could be ascribed to normalization of the extracellular to intracellular ratio of the cation. The problem is further complicated by the fact that the A-V delay occurs largely in the fibers of the conduction system.[5] Consequently, changes involving A-V conduction are related not only to myocardial potassium, but also to the intracellular to extracellular levels of potassium within the fibers of the A-V conduction system. In studies in which extracellular potassium was first lowered with insulin and glucose, and then potassium phosphate was infused to A-V block, the results suggested very strongly that the A-V delay and block was related primarily to the extracellular level of the cation.[6] There is no reason to assume that the A-V block induced by potassium was mediated entirely through the vagus. Blocking the vagus with large doses of atropine did not interfere with the production of A-V block by potassium (unpublished observations).

The transient elimination of acetyl-strophanthidin-induced arrhythmias by potassium appeared to be related to an increased extracellular level of the cation rather than to any specific potassium-digitalis antagonism. The depression of the arrhythmia by potassium was short lived, and the arrhythmia recurred when the average level of plasma potassium dropped from 6.4 to 5.4 mEq./L.

The observation that the arrhythmia produced by acetyl-strophanthidin was depressed at plasma levels (average, 6.4 mEq./L.) which were lower than those required to produce A-V block (average, 8.4 mEq./L.) should not be interpreted as supporting the concept of digitalis and potassium antagonism on the "arrhythmia" level. A similar sequence of depression of A-V conduction and ectopic beats has been observed in digitalized as well as nondigitalized human subjects with sinoatrial rhythm and ventricular premature beats. As a rule, ventricular premature beats are abolished without much difficulty, but prolongation of the P-R interval is noticed only occasionally and with what might be considered toxic doses of potassium.[1,2,9,10] It seems that the "focus" responsible for the arrhythmia is more sensitive to the depressing effects of potassium than is the A-V conduction tissue.

The total duration of the arrhythmia following the infusion of acetyl-strophanthidin and potassium (Study IV) was somewhat shorter than when acetyl-strophanthidin was given alone (Study I). This was due to overlapping of an elevated plasma potassium and the period of dissipation of acetyl-strophanthidin.

SUMMARY

1. The depression of A-V conduction and acetyl-strophanthidin-induced arrhythmia by intravenous potassium was transient; this finding was in agreement with similar observations made in human beings.

2. The observed effects of potassium can best be explained by elevation of the level of the cation in plasma rather than by any specific potassium-digitalis antagonism.

3. The supernormal phase of A-V conduction was demonstrated in an intact mammalian heart depressed by sodium pentobarbital and potassium.

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Transient Effect of Intravenous Potassium on A-V Conduction and Ventricular Ectopic Beats: Clinical Study

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Potassium salts for the treatment of cardiac arrhythmias were introduced by Sampson[1] in 1930, and have been used extensively since that time. Some workers have suggested that the salts are more useful in the management of ectopic rhythms due to digitalis than of those not associated with digitalis.[2,3] Bettinger[4] and his associates, after studying the relation of potassium to arrhythmias in 59 patients, stated that potassium was effective in 77 per cent of the cases of arrhythmias, ineffective in 17 per cent, and seemed to elicit ectopic beats in 6 per cent. This cation was found to be as effective in cases of arrhythmias associated with digitalis as in those not related to digitalis, and the authors did not believe that the response to potassium gives any information as to the genesis of the arrhythmia. They also observed that in patients with atrioventricular (A-V) conduction disturbances the effect of potassium on the conduction was to decrease the block, and the effect was often transient and could be varied by changing the rate of flow.

In the present study, we were particularly interested in extending our earlier observations made on 4 patients with atrial fibrillation and ventricular premature beats. At that time we noted that the administration of potassium resulted in a depression rather than acceleration of A-V conduction, and that the effect of potassium on ventricular ectopic beats was transient.[5] We thought that these observations, if confirmed, might explain the mechanism of the effect of potassium on ventricular premature systoles (VPS) and idioventricular rhythm (IVR).

METHOD

During the period of study of intravenous potassium and arrhythmias, the salt was administered intravenously 76 times to 60 patients with various forms of heart disease. Of the 60 patients, 16 form the basis of this report. They were selected because of persistent ventricular ectopic beats

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prior to infusion of potassium (12 patients) or the appearance of ventricular prematures after injection of the solution (4 patients). All but 2 had atrial fibrillation as an underlying rhythm. Patients 59 and 60 (Table I) exhibited sinus rhythm and atrial tachycardia with block, respectively.

After the patient had rested for 30 minutes, the potassium was administered intravenously in the form of isotonic solution (155 mEq./L.) of buffered potassium phosphate in distilled water. The rate of infusion was uniform for any given patient but varied in this series from 0.38 to 4.00 mEq. per minute. The speed of infusion was usually determined by the patient's tolerance of discomfort at the site of injection. A rapid injection for a period of 1 to 2 minutes at a rate of 3.0 mEq. per minute was attempted in each instance. This was not always possible because of severe pain at the site of infusion.

Most of the experiments were monitored with an oscilloscope; in others, an electrocardiogram (Standard Limb Lead II) was taken every 5 minutes, and continuously during the period of rapid infusion. All patients were observed for 2 hours after infusion was discontinued. The total amount of potassium administered varied from 4.0 to 40.0 mEq., but did not exceed 0.5 mEq. per kilogram of body weight in any of the subjects. The amount, the rate of infusion, the effect on A-V conduction, VPS and IVR, and the duration of this effect for each individual patient is presented in Table I.

RESULTS

Effect on Ventricular Premature Systoles.—In 9 of the 11 infusions the VPS were eliminated by potassium. In 6 individuals (Patients 8, 11-1, 20, 52, 57, 58) the VPS were abolished, with a parallel depression of conduction through the A-V node and resultant A-V dissociation or slowing of the ventricular rate (Figs. 1 and 2). In one case (Patient 59) the ventricular rate remained unchanged when the VPS were abolished, but shortly thereafter, complete heart block with unquestionable IVR appeared (Fig. 1). Infusions in Patient 11, on May 5 and May 12, 1958, resulted in elimination of VPS and a speeding of the ventricular rate (Fig. 3), even though on previous occasions marked slowing with A-V dissociation accompanied the disappearance of the VPS. The duration of depression of the VPS lasted up to 5 minutes after the intravenous infusion was discontinued. In many the presence or absence of ventricular ectopic beats depended entirely on the rate of flow of the solution. In Patient 2 the VPS were abolished "permanently," after first increasing in number. In the same individual the ventricular rate increased.

In Patient 57 the VPS persisted inspite of depression of A-V conduction to the point of complete A-V dissociation (Fig. 4). As a result of the infusion in Patient 49 the VPS not only increased but became multifocal.

Effect on Idioventricular Rhythm.—There were 4 individuals (Patients 5 42, 53, 58) in this group who exhibited IVR on control tracings; one of these patients also had runs of VPS (Patient 58). The IVR was abolished in all 4, with parallel slowing of ventricular conduction in 3 (Patients 5, 42, 58) and with speeding of the ventricular rate from 50 to 65 in 1 (Patient 53; Fig. 5). The depression of the IVR persisted from 2 to 35 minutes after the injection of potassium was stopped.

Appearance of Ventricular Ectopic Beats During the Infusion.—In 4 instances (Patients 25, 21, 50, 60) the VPS first became evident during the infusion of potassium. In one of these cases the appearance of an occasional VPS was preceded by cardiac standstill (Patient 60; Fig. 6).

TABLE I

PATIENT NUMBER	CONTROL RHYTHM	AMOUNT OF K INFUSED (mEq.)	RATE OF INFUSION (mEq./min.)	EFFECT OF K ON A-V CONDUCTION AND VENTRICULAR RATE			EFFECT OF K ON VENTRICULAR ECTOPIC BEATS	DURATION OF DEPRESSION OF VENTRICULAR ECTOPIC BEATS AFTER K STOPPED (MIN.)
				EFFECT ON A-V CONDUCTION	CONTROL VENTRICULAR RATE (INCLUDING ECTOPIC BEATS)	VENTRICULAR RATE DURING INFUSION (INCLUDING ECTOPIC BEATS)		
5.	AF, IVR	30.0	0.56	Slowing	68	45	IVR abolished	35
8.	AF, VPS	35.0	1.09	Slowing	70	55	VPS abolished	Transient
11–1. (Oct. 28, 1957)	AF, VPS	30.0	0.43	A-V dissociation	63	39	VPS abolished	Transient
11–2. (May 5, 1958)	AF, VPS	25.0	0.38	Speeding	90	80–118–95	VPS abolished	Transient
11–3. (May 12, 1958)	AF, VPS	10.0	2.00	Speeding	70	90	VPS abolished	Transient
20.	AF, VPS	30.0	2.00	Slowing	80	70	VPS abolished	Transient
42.	AF, IVR	35.0	0.50	A-V dissociation	70	60	VPS abolished	30
52.	AF, VPS	—	—	A-V dissociation	57	40	VPS abolished	5
53.	AF, IVR	33.0	1.83	Speeding	50	65	IVR abolished	5
58.	AF, VPS, IVR	40.0	0.80	Slowing	70	60	VPS and IVR abolished	2–5
59.	SR, VPS	15.0	1.00	A-V dissociation	70	70	VPS abolished	Transient
57.	AF, VPS	4.0	1.00	A-V dissociation	60	50	None	—
2.	AF, VPS	35.0	0.55	Speeding	65	70	VPS increased in numbers at first, and then abolished	"Permanent"
49.	AF, VPS	50.0	1.25	Speeding	60	100	VPS increased in number and became multifocal	—
25.	AF	7.0	2.70	Slowing then speeding	60	50–80	VPS first appeared during infusion	—
21.	AF	40.0	4.00	A-V dissociation	45	26	VPS first appeared after K	—
50.	AF	24.0	1.05	A-V dissociation	60	50	VPS and IVR first appeared during and after infusion, respectively	—
60.	PAT with block	4.25	0.65	Cardiac standstill	—	—	Occasional VPS after infusion	—

AF: Atrial fibrillation. IVR: Idioventricular rhythm. VPS: Ventricular premature systoles. PAT: Paroxysmal atrial tachycardia.

DISCUSSION

The series presented is not large in number but the effect was so uniform as to make our conclusions valid. In searching for subjects for this study we were surprised by the paucity of cases with ventricular ectopic beats that would satisfy the following criteria: (1) were associated with digitalis therapy, (2) were present on at least three tracings taken 12 to 24 hours apart, (3) were consistently present in any one tracing, and (4) did not disappear or diminish in number on rest.

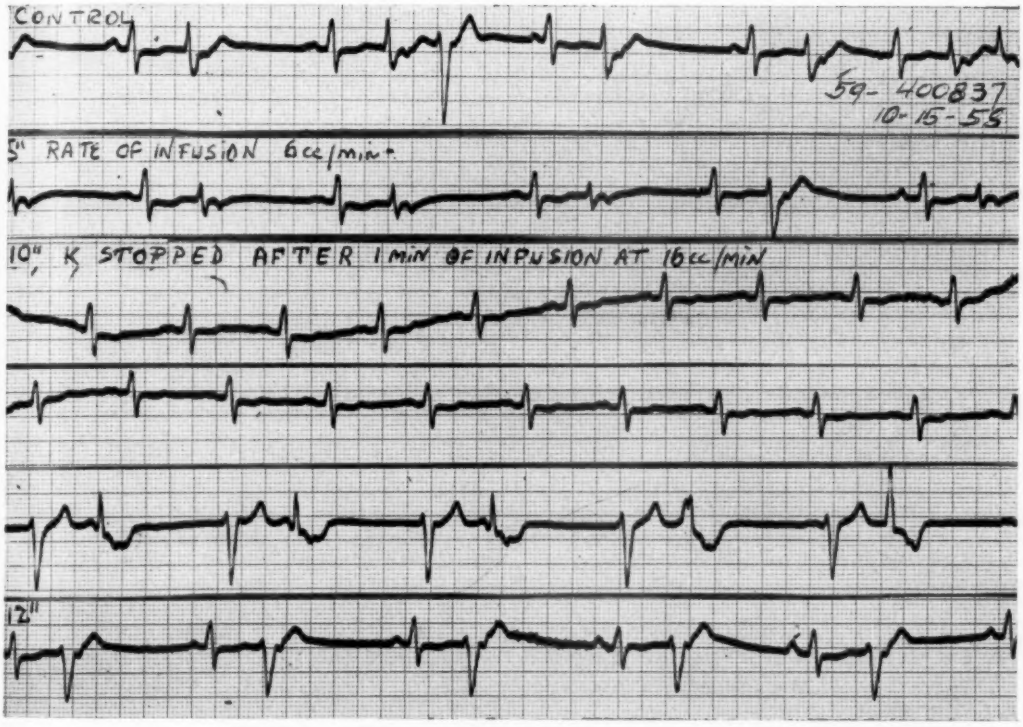

Fig. 1.—Patient 59. This tracing demonstrates the parallel depression of ventricular premature beats and A-V conduction. The numbers in the upper left corner of the strips denote time in minutes from start of infusion. This convention, unless otherwise noted, will be adhered to in all tracings. The control tracing shows a basic sinoatrial rhythm with ventricular bigeminy and retrograde conduction to the atria as manifest by inverted P waves following the ectopic beats. Ventricular complexes 5 and 12 may represent reciprocal beating. The retrograde conduction is quite obvious in the second strip. After 1 minute of infusion at a rate of 2.7 mEq. (10-minute strip) the VPS disappear and a complete A-V dissociation appears, with aberrant idioventricular rhythm and bigeminy (strips 3, 4, 5). Sinus rhythm with ventricular bigeminy is re-established promptly upon cessation of infusion (strip 6).

We purposely avoided infusion of "control" solutions in order not to add another variable. Furthermore, we felt that buffered phosphate was less likely to alter acid-base balance than would chloride. Infusion of sodium phosphate to dogs, in amounts three times that of potassium phosphate needed to produce A-V block, was without any effect on the electrocardiogram.[6]

It is extremely difficult, if not impossible, to state unequivocally that a ventricular arrhythmia, regardless of its complexity, is due to digitalis. Many

so-called "typical" cases of digitalis bigeminy or multifocal premature beats are an expression of myocardial disease and persist after the drug is discontinued. Unless an arrhythmia appears during digitalis therapy, and an obvious overdose of the drug can be demonstrated, such arrhythmias cannot and should not, for research purposes, be attributed to digitalis. Unless strict criteria are used in selecting patients for the study of antiarrhythmic drugs, the results will often be misleading, and a host of new "better" antiarrhythmic compounds will appear on the market. In all of our patients the arrhythmia was consistently present during the control period; thus, the depression of ectopic beats by 12 of the 14 infusions can be safely ascribed to potassium.

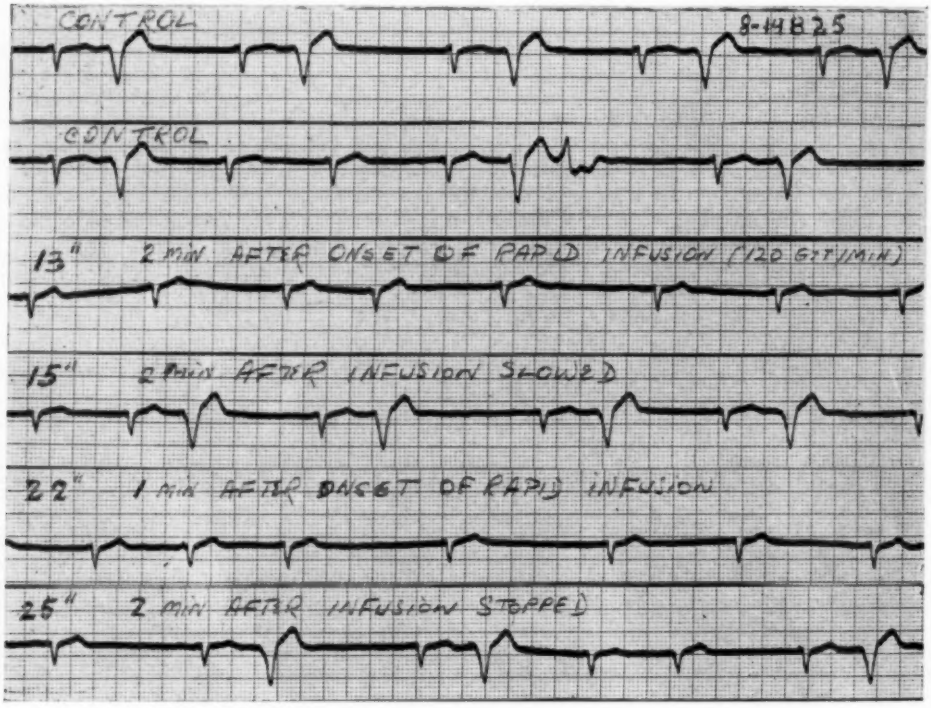

Fig. 2.—Patient 8. This tracing is representative of the transient effect of potassium on the ventricular premature beats. The control tracing (strips 1, 2) shows atrial fibrillation with VPS. The latter are abolished by two separate rapid infusions (strips 3, 5). The ventricular premature beats reappear each time within 2 minutes after injection is stopped (strips 4, 6).

We were surprised by the transient effect of potassium on the VPS and IVR. Although the VPS were abolished in 12 of 14 experiments, their reappearance in all but one (Patient 2) was prompt upon discontinuation of the infusion. In some patients, their presence and absence could be regulated merely by changing the rate of infusion. A similar transient effect on A-V conduction was observed in human subjects with sinus rhythm,[7,8] atrial fibrillation,[5] and atrial flutter.[4]

The fleeting effect observed is hardly compatible with a notion that the beneficial effect of potassium in the treatment of ectopic rhythms accompanying

digitalis therapy is due to the replacement of the cation. That depletion of potassium exists in some cases of congestive failure and digitalis intoxication is well documented.[9-15] This depletion could be exogenous in character: due to nausea, vomiting, poor appetite, or excessive loss of weight; due to indiscriminate diuretic therapy; or due to underlying cardiovascular disturbance aggravated perhaps by digitalis intoxication. It is difficult to accept the notion that potassium alone, without parallel correction of the mechanism responsible for hypokalemia, will result in the retention of potassium and the control of signs and symptoms of digitalis intoxication. It is more likely that the effect of potassium is a result of depression of the ectopic focus by a transient elevation of the plasma level of the cation rather than any specific digitalis-potassium "antagonism." Such an

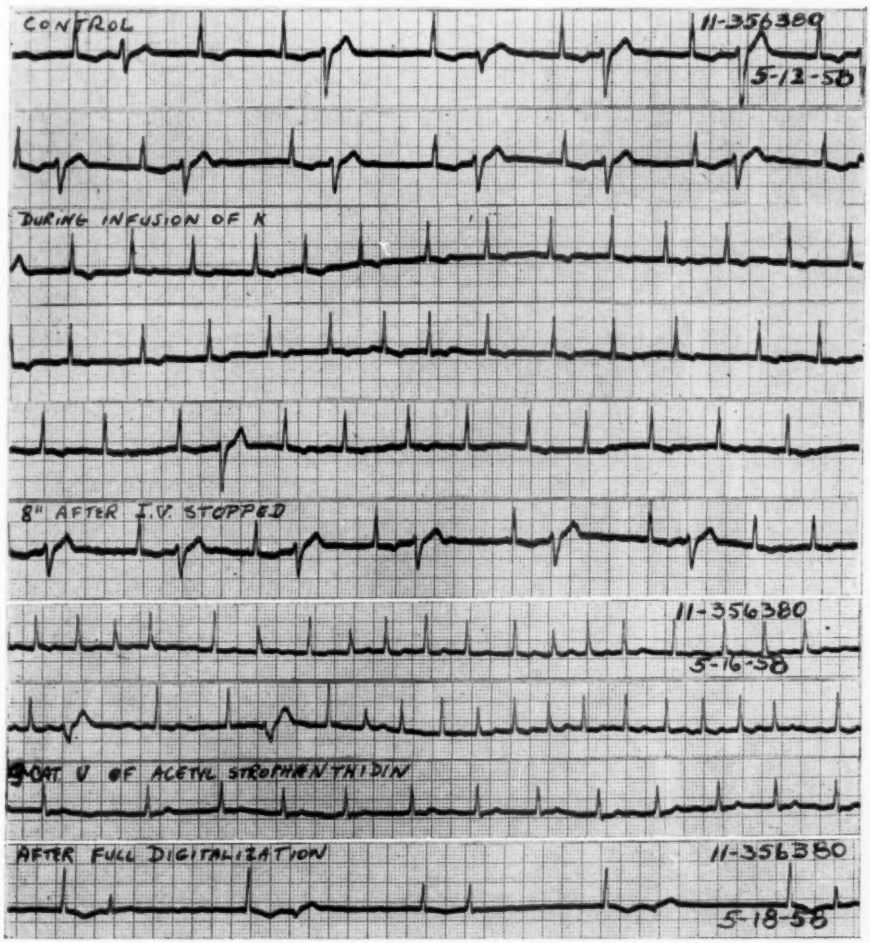

Fig. 3.—Patient 11. Tracings *A*, *B*, *C*, taken on May 12, 16, and 18, 1958, exemplify the effect of potassium in a patient incompletely digitalized. *A* shows the elimination of VPS, with a parallel acceleration of the ventricular rate. *B* confirms the incomplete digitalization by demonstrating a slowing of ventricular rate from about 150 to 80 following the administration of 9 cat units of acetyl-strophanthidin. *C* was taken after digitoxin was administered, and resembles an electrocardiogram obtained on this patient on Oct. 28, 1959, at which time the response to intravenous potassium was one of depression of A-V conduction (see text for details).

explanation is supported (1) by Bettinger's[4] experience that ventricular premature beats not related to digitalis were abolished by this cation in a manner similar to that of those "due to" digitalis, (2) by observation that the A-V conduction is usually depressed when ventricular ectopic beats are eliminated,[5,18] and (3) by animal studies in which it was possible to demonstrate a comparable transient depression of ventricular tachycardia and A-V conduction by potassium.[6]

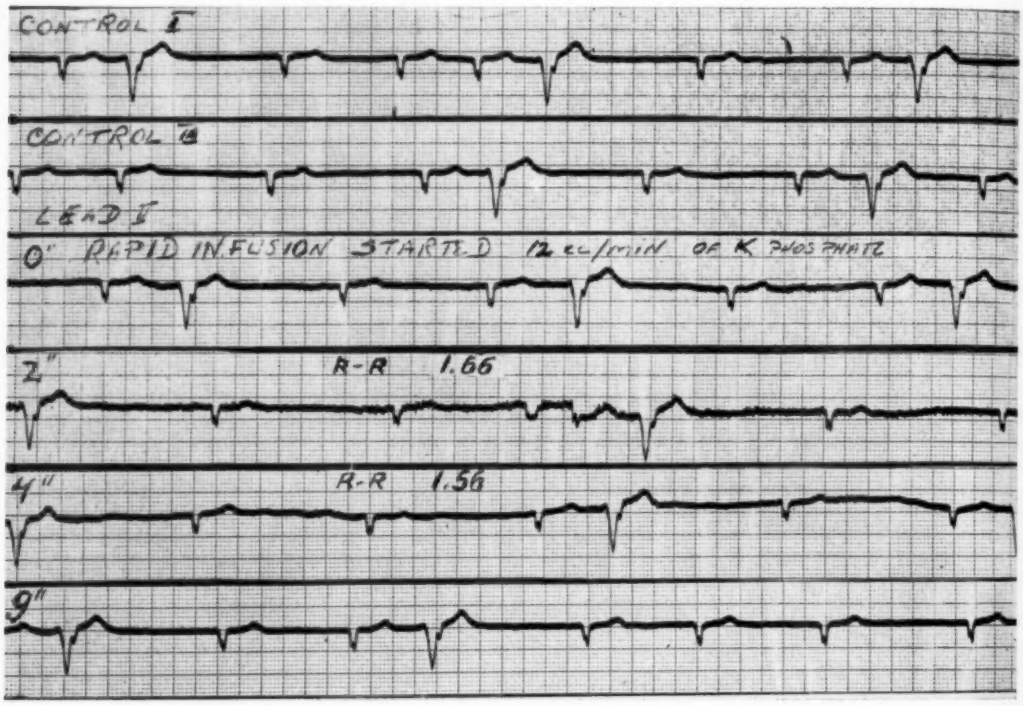

Fig. 4.—Patient 57. This tracing is an example of depression of A-V conduction but without any effect on the VPS. The control tracing (strips 1, 2) shows atrial fibrillation with VPS. The latter did not disappear despite depression of A-V conduction to complete A-V dissociation with R-R intervals of 1.66 and 1.56 seconds (strips 4, 5). Strip 6, taken shortly after the infusion was stopped, is identical to the control tracing.

The failure to find an elevated serum potassium at the time of depression of both the A-V conduction and ectopic beats does not invalidate the suggested explanation of the action of potassium salts. The effects of potassium on the myocardium is a function of the intraventricular and intramyocardial concentration of the cation, and as such cannot be determined by sampling potassium from the peripheral circulation. The inherent danger in giving intravenous potassium is that, without cardiac catheterization, the intraventricular level cannot be determined. In the presence of an increased residual ventricular blood volume this cation can conceivably reach dangerous levels. We believe that the latter situation could explain the mechanism responsible for the cardiac standstill in Patient 60 (Fig. 6).

The increased number of ectopic beats or their initial appearance after

potassium was previously observed by Bettinger.[4] The exact mechanism is difficult to elucidate, although local blocks and slowed conduction result in increased automaticity.[16,17]

The speeding of the ventricular rate in Patients 2 and 11 during infusion is probably due to the sympathetic effect on the A-V conduction in a partially digitalized individual. The sympathetic stimulation was probably brought on by the pain at the site of injection, anxiety, or nausea. This may perhaps explain the increase in A-V conduction observed by Bettinger in his patients with atrial flutter.[4] A similar speeding, rather than slowing, of the ventricular rate was observed by us in other patients with atrial fibrillation (not included in this study) who were believed not to be fully digitalized. Patient 11, a 37-year-old woman with severe mitral stenosis, exemplifies the effect of potassium in an undigitalized individual (Fig. 3,*A*). On May 12, 1958, after the administration of potassium the ventricular rate speeded up and VPS were abolished. On May 15, 1958,

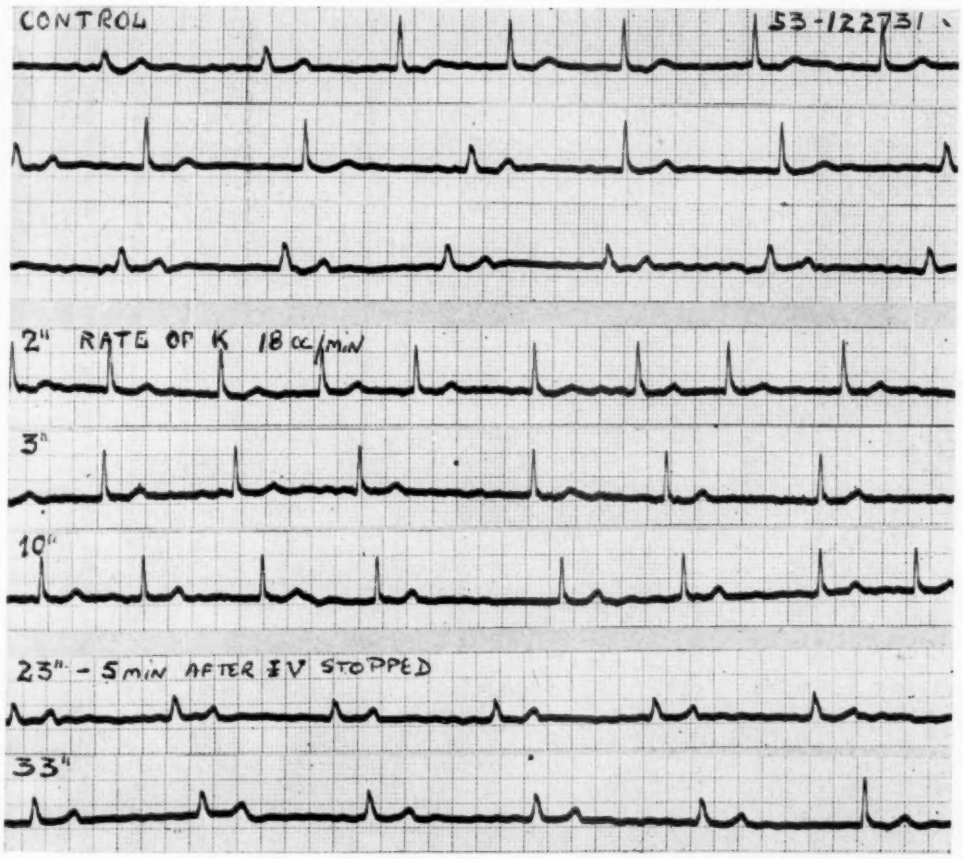

Fig. 5.—Patient 53. This tracing demonstrates the effect of potassium on IVR. The control tracing (strips 1, 2, 3) shows atrial fibrillation with runs of IVR or ventricular escape beats. These were eliminated during infusion of potassium (strips 3, 4, 5). The IVR reappeared within 5 minutes after the administration of potassium was discontinued (strip 7). Many of the R-R intervals of supraventricular beats during infusion were longer than the R-R intervals of the idioventricular beats, indicating that the IVR was eliminated by the direct depressing effect of potassium rather than by increased conduction from the atrium.

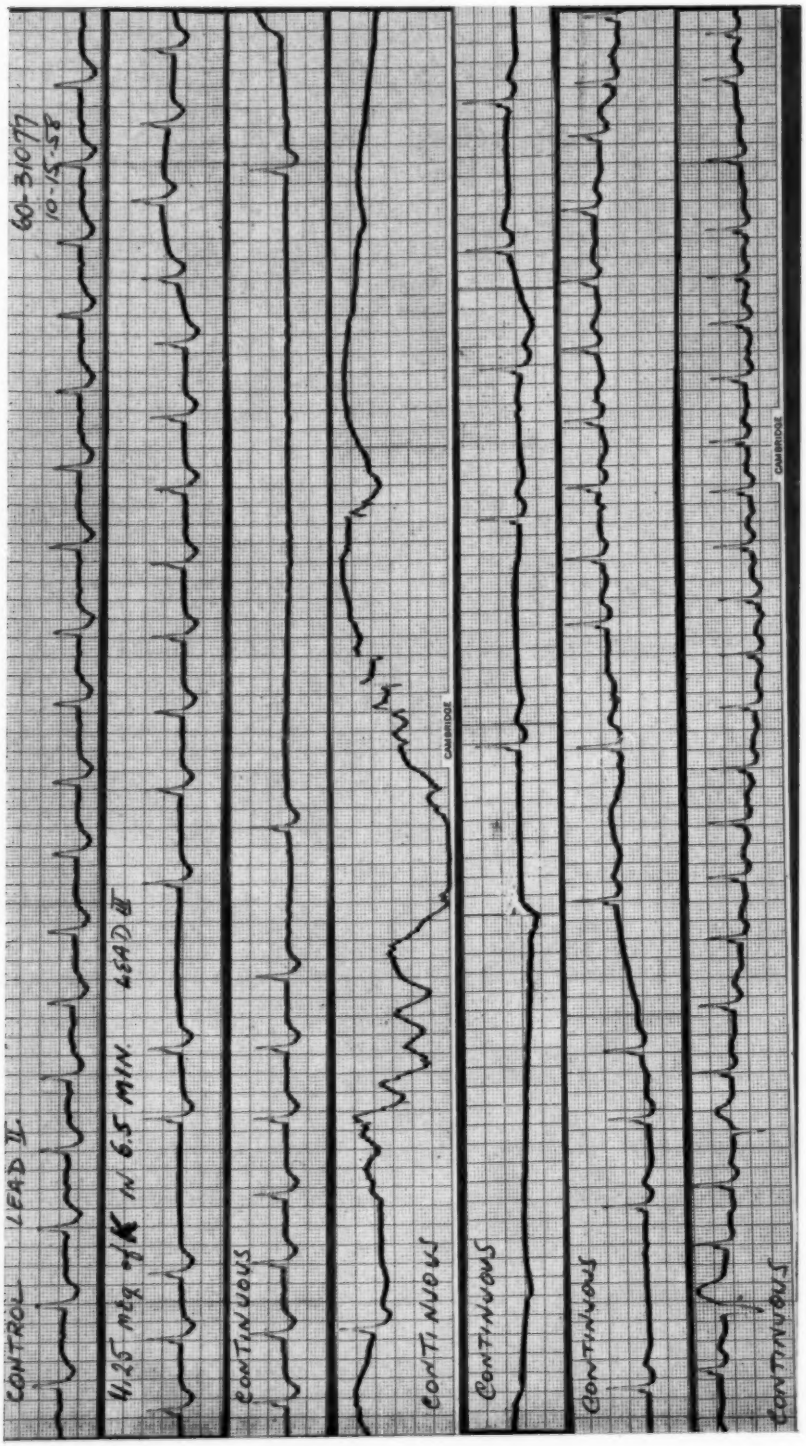

Fig. 6.—Patient 60. This tracing demonstrates cardiac arrest as well as occasional VPS appearing after infusion of potassium. The control tracing demonstrates what we considered to be paroxysmal atrial tachycardia with block. Infusion of 4.25 mEq. of potassium at a rate of 0.65 mEq. per minute resulted in cardiac standstill.

the patient was found to be in severe left ventricular failure, with a ventricular rate of about 150 beats and pulse deficit of approximately 90 beats per minute; with acetyl-strophanthidin the rate slowed to 80 beats per minute (Fig. 3,*B*), indicating incomplete digitalization. With increasing doses of digitoxin, full digitalization was accomplished by May 18, 1958 (Fig. 3,*C*). The latter tracing resembles one recorded on Oct. 28, 1957, at which time it was observed that slowing of the ventricular rate paralleled elimination of VPS (Reference 5; Fig. 3). It is our feeling that the speeding of the ventricular rate in patients with atrial fibrillation and flutter, as a result of the infusion of potassium, is an expression of incomplete digitalization. Proof of this concept must await further study.

In our hands, the short-lived elimination of ventricular ectopic beats, coupled with A-V and myocardial depression, does not justify routine use of intravenous potassium in the treatment of ventricular arrhythmias.

SUMMARY

1. Fourteen infusions of potassium phosphate to 12 digitalized individuals with persistent ventricular ectopic rhythms resulted in a transient depression of the ectopic focus in 12 experiments. In one there was no effect and in another the ventricular premature beats increased in number during the infusion. In 4 additional patients the ventricular ectopic beats first appeared during or after the infusion.

2. Depression of A-V conduction with resultant slowing of the ventricular rate was observed during 11 of the 18 infusions.

3. The parallel depression of A-V conduction and the ectopic ventricular foci suggests that the effect of potassium is one of myocardial depression. Furthermore, the short-lived beneficial effect of potassium suggests that the mechanism may be due to a transient elevation of the extracellular level of the cation.

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Experimental and Laboratory Reports

The Effect of Alterations in Arousal of the Central Nervous System Upon Cardiovascular Response to Intravenous Epinephrine

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Recent observations have demonstrated that the changes in cardiovascular function which accompany experimentally induced alterations in affect are similar to those which follow the infusion of epinephrine. It is notable that epinephrine produces an anxiety state comparable to that experienced by the individual subjected to experimental stress.[1] These observations suggested a further study of the relationship between activity of the central nervous system and cardiovascular function mediated by epinephrine. It is the specific purpose of this study to examine the effect of alteration in the status of arousal of the central nervous system upon the cardiovascular response to epinephrine.

METHODS AND SUBJECTS

Twenty-two young male volunteer subjects were studied in the supine position and post-absorptive state. Cardiac output was determined by the indicator dilution technique, using T-1824 and superior vena caval catheterization with the serial collection of timed (2 sec.) arterial samples as previously described.[2,3] Arterial and central venous pressure were monitored by Statham strain gauge transducers and were electronically integrated. Respiratory rate and excursion were recorded by a pneumotachograph. The heart rate was measured from a standard limb electrocardiograph.

In 12 subjects, cardiac output and other determinations were made in this sequence: (1) a resting control state, (2) immediately after administration of 10 gamma (10 γ) of epinephrine intravenously, (3) 20 minutes to one-half hour after administration of 800 mg. of meprobamate† dissolved in 200 c.c. of physiologic sodium chloride solution, which was injected intravenously over a 5-minute period, and (4) after a second dose of 10 gamma of epinephrine intravenously.

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TABLE I. CARDIOVASCULAR MEASUREMENTS IN A SERIES OF 10 SUBJECTS RECEIVING SALINE DURING THE COURSE OF THE MORNING

SUBJECTS	CONTROL							"PSEUDO-EPINEPHRINE"						AFTER SALINE						"PSEUDO-EPINEPHRINE-SALINE"					
	B.S.A. ($M.^2$)	C.I. ($L./MIN./M.^2$)	MCT (SEC.)	CBV (L.)	HR (BEATS/MIN.)	SV (ML.)	MAP (MM. Hg)	C.I. ($L./MIN./M.^2$)	MCT (SEC.)	CBV (L.)	HR (BEATS/MIN.)	SV (ML.)	MAP (MM. Hg)	C.I. ($L/MIN./M.^2$)	MCT (SEC.)	CBV (L.)	HR (BEATS/MIN.)	SV (ML.)	MAP (MM. Hg)	C.I. ($L./MIN./M.^2$)	MCT (SEC.)	CBV (L.)	HR (BEATS/MIN.)	SV (ML.)	MAP (MM. Hg)
I	2.00	2.41	20.8	1.67	68	63	95	2.63	18.9	1.66	72	73	—	2.95	19.3	1.90	70	84	95	2.95	18.1	1.78	72	82	95
II	2.01	2.61	19.9	1.74	63	83	96	2.71	19.9	1.80	60	90	98	2.83	18.3	1.73	66	86	100	2.92	19.7	1.93	66	89	97
III	1.53	3.28	15.0	1.26	68	74	78	2.97	17.6	1.33	74	61	76	3.85	13.7	1.35	62	95	84	4.54	13.1	1.52	64	108	80
IV	1.87	2.64	20.8	1.71	55	90	75	2.54	18.8	1.49	54	88	80	3.35	17.0	1.77	57	109	84	3.21	17.4	1.74	54	111	84
V	1.99	3.19	15.8	1.67	61	104	70	3.00	16.6	1.65	63	95	70	3.60	15.1	1.80	63	114	70	3.59	15.1	1.80	63	113	70
VI	1.96	3.08	16.6	1.67	60	100	85	3.14	14.6	1.50	64	97	80	2.97	15.5	1.51	66	88	85	—	—	—	—	—	—
VII	2.05	2.87	16.8	1.65	60	98	85	2.90	16.9	1.68	60	99	92	2.91	17.9	1.78	60	99	90	3.25	17.3	1.92	63	106	95
VIII	1.91	2.98	17.4	1.65	60	95	85	3.08	16.6	1.63	65	91	80	3.58	15.6	1.78	62	110	80	3.73	14.9	1.82	66	111	90
IX	1.94	2.82	16.5	1.51	52	105	75	2.85	19.0	1.75	52	106	75	3.17	18.5	1.89	60	102	70	4.20	16.6	2.26	57	143	70
X	1.93	3.18	20.6	2.11	65	94	80	3.26	21.1	2.21	64	98	80	3.29	18.2	1.93	64	99	80	3.46	16.9	1.88	62	108	80
Average		2.91	18.0	1.66	61	91	82	2.91	18.0	1.67	63	90	81	3.25	16.9	1.74	63	99	84	3.54	16.6	1.85	63	108	85

B.S.A.: Body surface area. C.I.: Cardiac index. MCT: Mean circulation time. CBV: Central blood volume. HR: Heart rate. SV: Stroke volume. MAP: Mean arterial pressure.

TABLE II. CARDIOVASCULAR MEASUREMENTS IN A SERIES OF SUBJECTS ADMINISTERED EPINEPHRINE BEFORE AND AFTER INFUSION OF MEOPROBAMATE

SUBJECTS	CONTROL							EPINEPHRINE ALONE					MEPROBAMATE						EPINEPHRINE-MEPROBAMATE				
	B.S.A. ($M.^2$)	C.I. (L./MIN./$M.^2$)	MCT (SEC.)	CBV (L.)	HR (BEATS/MIN.)	SV (ML.)	MAP (MM. Hg)	C.I. (L./MIN./$M.^2$)	MCT (SEC.)	CBV (L.)	HR (BEATS/MIN.)	SV (ML.)	C.I. (L./MIN./$M.^2$)	MCT (SEC.)	CBV (L.)	HR (BEATS/MIN.)	SV (ML.)	MAP (MM. Hg)	C.I. (L./MIN./$M.^2$)	MCT (SEC.)	CBV (L.)	HR (BEATS/MIN.)	SV (ML.)
I	1.90	2.4	20.9	1.58	63	72	—	5.6	11.1	2.00	105	102	2.3	23.9	1.70	63	69	—	3.2	20.0	2.00	68	88
II	1.85	3.7	15.0	1.71	78	88	84	4.5	12.7	1.60	84	98	3.4	17.1	1.80	72	88	83	4.7	13.1	1.90	82	107
III	1.65	3.0	17.4	1.41	66	74	80	5.2	11.0	1.57	90	95	3.1	17.8	1.50	75	68	85	6.7	8.1	1.49	105	105
IV	1.93	3.0	22.8	2.20	64	90	90	5.7	12.2	2.24	111	99	3.2	20.8	2.16	81	77	86	4.5	15.9	2.30	105	82
V	1.97	3.7	15.6	1.91	69	106	90	4.9	10.9	1.76	90	108	4.6	13.4	2.03	69	132	100	5.6	10.0	1.84	93	119
VI	1.72	3.3	13.7	1.28	81	70	70	4.7	10.7	1.43	96	83	3.5	14.2	1.41	84	71	72	4.7	11.5	1.53	96	83
VII	1.93	4.3	14.7	2.05	78	107	72	5.9	10.2	1.95	111	103	4.2	14.0	1.90	78	104	72	6.8	9.8	2.13	105	124
VIII	1.64	3.5	16.5	1.58	63	91	80	6.0	8.7	1.44	120	83	3.0	20.2	1.66	66	66	82	7.6	9.7	2.00	105	118
IX	2.03	3.2	18.1	1.97	72	91	76	4.6	13.4	2.08	90	104	3.1	18.4	1.90	68	91	70	6.7	12.6	2.85	89	152
X	1.87	2.9	19.3	1.74	63	86	58	5.8	9.9	1.78	102	106	2.7	19.9	1.66	68	74	63	5.5	10.4	1.77	96	107
XI	1.78	2.6	23.9	1.82	51	90	75	5.2	12.4	1.90	84	109	2.8	21.6	1.78	65	76	80	3.9	19.5	2.26	66	105
XII	1.82	2.9	17.8	1.54	—	—	—	5.0	10.1	1.54	—	—	3.1	18.0	1.67	—	—	—	7.3	9.3	2.05	—	—
Average		3.2	18.0	1.73	68	88	78	5.2	11.1	1.77	98	99	3.3	18.3	1.76	71	83	79	5.6	12.5	2.00	92	108

B.S.A.: Body surface area. C.I.: Cardiac index. MCT: Mean circulation time. CBV: Central blood volume. HR: Heart rate. SV: Stroke volume. MAP: Mean arterial pressure.

Ten additional subjects were used for control observations in which the entire procedure was simulated using sodium chloride for injection, rather than drugs, without prior knowledge of the subject.

Meprobamate, a "central relaxant," is not known to have specific primary circulatory action.[4a,4e,4f,5-7] At a dosage level of 800 mg. of meprobamate, electroencephalographic changes are detected, and were observed in our laboratory. The 800 mg. dose of meprobamate has also been considered of sufficient magnitude to produce a "tranquilizing effect."[4a] Previous experience has indicated that a 15- to 20-minute latent period occurs before the parenterally administered meprobamate exerts its tranquilizing effect.[4e]

RESULTS

Table I records the cardiac output, arterial blood pressure, and pulse rate on subjects observed during control procedure in which four measurements of cardiac output were performed with isotonic sodium chloride substituted for the drugs used in the other observations. These subjects reported no significant change in feeling state or affect during the procedure. It was observed, however, that there was some slight increase in restlessness as the study proceeded. These control subjects showed no significant variation in the circulatory functions observed. The average cardiac index, using all determinations, was 3.2 L./min./M.^{2} (range, 2.4 to 4.1).

The observations on the subjects receiving the actual epinephrine-meprobamate sequence are recorded in Table II and Fig. 1. In this group of subjects, there was an average control cardiac index of 3.2 L./min./M.^{2} (range, 2.4 to 4.3). The average control pulse rate for this group was 68 per minute, with an average stroke volume and mean arterial pressure of 88 c.c. and 78 mm. Hg, respectively. The average control central blood volume was 1.73 L.

The cardiac index immediately following the first injection of epinephrine averaged 5.2 L./min./M.^{2} (range, 4.5 to 6.0), representing an average increase of 60 per cent over the control level. The average pulse rate recorded in response to epinephrine was 98 per minute with a stroke volume of 99 c.c. The central blood volume at this same time was measured as 1.77 L., showing no change from that in the control state.

After the infusion of meprobamate, all subjects reported a feeling of relaxation, a decrease in perceptivity and awareness, and a diminution in the usually dramatic subjective effects of the epinephrine injection. Subjects who received saline perceived no changes in arousal.

The cardiac output measured after the administration of meprobamate revealed no change as compared to the first or control determination ($p = 0.9$). There was also no significant change in the heart rate, stroke volume, mean arterial pressure, and central blood volume during these two periods.

The response of cardiac output to the second injection of epinephrine gave an average cardiac index of 5.6 L./min./M.^{2} (range, 3.2 to 7.5), which is an average increase of 74 per cent over the control and the meprobamate cardiac outputs. The response following this second injection of epinephrine is slightly higher than the first epinephrine output, but this is not statistically significant ($p = 0.1$). The responses of the heart rate and stroke volume were essentially the same to both injections of epinephrine. However, the central blood volume was calculated

to be 2.0 L. at the time of the second injection of epinephrine, representing an increase of 230 c.c. over that measured during the first stimulation by epinephrine, a variation within the error of the method.

From the results of this study we were unable to detect any significant circulatory response to meprobamate alone or attenuation in the response to epinephrine after administration of meprobamate as compared with the two control levels. The subjects detected less subjective excitatory effects of epinephrine after administration of meprobamate at the same level of cardiac response. This may be related to the altered activity of the central nervous system induced by meprobamate or familiarity with the expected stimuli.

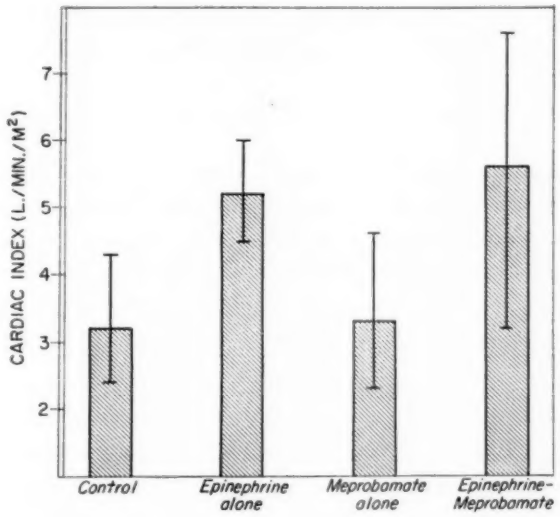

Fig. 1.—Mean cardiac index in subjects receiving epinephrine intravenously before and after meprobamate.

DISCUSSION

Emotional or stress-induced situations, commonly interpreted as resulting in anxiety, are associated with increased circulatory activity. The hemodynamic response usually indicates an epinephrine-like effect. Previous observations in this laboratory have shown this also to be produced by stimuli which alter the affective state of the central nervous system.[1] Whether such a response is dependent upon the degree of reactivity of the central nervous system or occurs independently is of importance. It is conceivable that the subjective feelings interpreted as anxiety are a consequence of the associated somatic reactions (increased blood pressure, pulse rate, sweating, etc.) which produce effects on cerebral activity. An alternative hypothesis would be that a primary central nervous system response occurs, with the general systemic reaction following as an integral, but not as an initiating, factor in this important chain of events.

The introduction of meprobamate appeared to afford the opportunity to analyze further the interrelationships of this mechanism. Meprobamate belongs to that group of tranquilizing agents known as "central relaxants."[4a,6] It acts primarily on the thalamus. It apparently blocks interneuronal circuits and

exaggerated reflexes and is able to produce reversible paralysis of voluntary muscles without significantly affecting autonomic functions.[6] The drug is not known to have a specific action upon the circulatory system.[4d-6] Even in toxic doses, in cases of attempted suicide, the patients have maintained normal blood pressure, pulse rate, and oxygen exchange despite stupor and hyporeflexia.[4d]

The results of the study indicate that the hemodynamic response to epinephrine is unaltered by pharmacologically effective doses of meprobamate. The doses used were sufficient to alter cerebral activity as demonstrated by electroencephalographic changes in these studies. Therefore, we have concluded that alteration in arousal of the central nervous system produced by meprobamate does not modify the response of the circulation to epinephrine. Whether other methods of altering activity of the central nervous system, such as hypnosis and sleep, affect responsivity to epinephrine is open for further study.

SUMMARY AND CONCLUSIONS

(1) Measurements of cardiac output, heart rate, and central blood volume were made in 12 subjects both before and immediately after the intravenous administration of epinephrine during altered states of central nervous system arousal. (2) Arousal of the central nervous system was altered by the administration of 800 mg. of meprobamate intravenously. (3) Response to epinephrine was not modified by this induced change in arousal.

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Response of the Coronary Arterial Bed to Electroshock: An Experimental Study in Dogs

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Most fatalities associated with electroconvulsive therapy (ECT) are caused by acute cardiovascular strain. According to Tewfik and Wells,[1] whose data are in part an extension of an earlier study by Maclay,[2] the fatalities associated with electroconvulsive therapy in psychiatric hospitals in England and Wales during the period 1947 through 1955 showed that 73 per cent of all such deaths were due to cardiovascular causes. Of the 66 deaths attributable to cardiovascular complications during this 8-year interval, approximately 26 per cent were due to coronary thrombosis. The remaining 74 per cent were listed as having been caused by sudden cardiac failure.

From a smaller series of patients, Alexander, Gahagan and Lewis[3] have reported findings which suggest that coronary dysfunction may be implicated in ECT fatalities even when thrombosis does not occur. From a total of 5,325 patients treated in a 6-year period, 5 died during or shortly after ECT. Four of these patients were autopsied. In 1 patient, a fresh coronary thrombus was found; in all 4 patients there was evidence of coronary sclerosis and insufficiency. Marked hemodynamic changes occur after ECT, and might be expected to place an additional strain on a diseased coronary bed.

It is well established that the typical cardiovascular response to an electrically induced convulsion is biphasic, and consists of (1) a brief period of bradycardia and hypotension, which is followed by (2) a period of tachycardia and rise in blood pressure, the pressure remaining elevated for 5 minutes or more.[4,5] Holmberg and his associates[6] found that the rise in the mean arterial pressure over the control level averaged 87.9 mm. Hg when no skeletal muscle relaxant

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was given; when the patient was given succinylcholine prior to treatment, the rise in mean pressure above control levels averaged 64.4 mm. Hg. In the dog,[4] monkey,[7] and man[8] the response of arterial pressure to electrically induced convulsions assumes the same general pattern. This permits the ready application of the studies with dogs to human beings.

In previous experiments on anesthetized dogs in these laboratories[5] it was found that the cardiovascular response could be reproduced repeatedly in the same dog if sufficient time was allowed for the arterial pressure to return to the control level after electrical stimulation. By repeating electrical stimulation at appropriate time intervals and interspersing doses of autonomic blocking drugs or surgical procedures (vagotomy, adrenalectomy, cervical cord section), it was concluded that the cardiovascular response is due to a generalized discharge of both branches of the autonomic nervous system following the electrical stimulus. Cholinergic mechanisms prevail during the first brief portion of the response and cause bradycardia and hypotension; in the second portion of the response, adrenergic mechanisms predominate and bring about a rise in arterial pressure, an increased cardiac contractile force, and peripheral vasoconstriction. The same general experimental design has been used for studying the coronary effects of experimental electroshock in the dog.

METHODS

Dogs of both sexes were anesthetized with pentobarbital (Nembutal), 30 mg./Kg. intraperitoneally. A sinusoidal stimulus of 150-volt intensity and 1-second duration was delivered by a Medcraft ECT unit to the dog through temporal electrodes fastened to the dog's head with bandage, electrode jelly being used to ensure proper contact. Previous studies had shown that a stimulus of this intensity was supramaximal in terms of the cardiovascular response.[9] The stimulus was applied at 15-minute intervals. This interval allowed time for recovery; the arterial pressure returned to its control level and similar cardiovascular responses were evoked by the succeeding stimulations. Succinylcholine chloride (Anectine) in dosage of 0.3 mg./Kg. was administered 90 seconds prior to each stimulation; this eliminated any cardiovascular effects due to skeletal muscle contraction. This procedure in dogs, which is analogous to modified electroconvulsive therapy in human beings, has been referred to previously as transcranial stimulation, or TCS.[5,9,10]

For recording of the various cardiovascular responses, appropriate pressure transducers, flowmeters, and strain gauges were used in connection with a Sanborn Poly-Viso recorder. Systemic arterial pressure was registered from a cannulated carotid artery. All drugs were administered by a cannula in the left femoral vein. Changes in cardiac contractile force were measured by means of a Walton strain gauge arch,[11] which was sutured to the surface of the left ventricle. Positive pressure artificial respiration with a Starling "Ideal" pump was applied continuously through a tracheal cannula.

Changes in coronary flow were recorded in the following manner. The left femoral artery was cannulated cardiad, and blood was led through polyethylene tubing to a Shipley-Wilson rotameter,[12] and from there to a cannula inserted into the anterior descending coronary artery or into one of its branches. Changes in coronary resistance were calculated in terms of peripheral resistance units (PRU) by dividing the flow in milliliters per minute into the mean arterial pressure. As a check on these measurements, changes in coronary resistance were also determined by recording the changes in perfusion pressure when the anterior descending coronary artery or branch was being perfused with blood at a constant rate of flow with a Sigmamotor pump. Changes in perfusion pressure were recorded by a transducer connected to the perfusion line. In 8 dogs in which measurements of perfusion pressure were made, left femoral arterial blood was led directly to the pump.

In 4 additional dogs the pump was supplied with blood from a small open reservoir during the period of measurement. Since the values obtained by the two methods did not differ in either extent or direction, they have been averaged together.

RESULTS AND DISCUSSION

The values for coronary flow in Table I were obtained from duplicate determinations in each of 8 successful experiments, and those for coronary perfusion pressure, from duplicate determinations in each of 12 successful experiments. The values for arterial pressure and relative cardiac contractile force as determined by the Walton strain gauge arch have been averaged from both types of experiment. For convenience in discussion, the initial vagal phase after electrical stimulation, during which the heart slows or stops and the blood pressure falls, has been designated as the hypotensive phase. The immediately ensuing period, during which the blood pressure rises and cardiac contractile force increases, has been designated the hypertensive phase.

TABLE I. THE EFFECTS OF ELECTROSHOCK ON SEVERAL PARAMETERS OF CARDIAC PHYSIOLOGY

PARAMETERS	CONTROL	HYPOTENSIVE PHASE	HYPERTENSIVE PHASE
Arterial Pressure (S/D)* (mm. Hg)	120/95	−/70†	170/135
maximum effect reached (sec.)	—	2	15
duration of effect (sec.)	—	4	466
Relative Cardiac Contractile Force‡ (mm.)	23	0	30
maximum effect reached (sec.)	—	0	19
duration of effect (sec.)	—	2	294
Coronary Flow (ml./min.)	21	19	28
maximum effect reached (sec.)	—	2	17
duration of effect (sec.)	—	3	252
peripheral resistance units (PRU)	4.9	3.7	5.3
Coronary Perfusion Pressure (mm. Hg)	110	90	120
maximum effect reached (sec.)	—	2	13
duration of effect (sec.)	—	7	12
Coronary Perfusion Pressure after atropine sulfate 0.5 mg./Kg.	105	105	120
maximum effect reached (sec.)	—	—	9
duration of effect (sec.)	—	—	14

*S/D = Systolic/Diastolic.
†Heart asystolic.
‡Cardiac contractile force as measured by the Walton gauge.

In a given situation the coronary flow is dependent on the height of the arterial pressure and the resistance to flow offered by the vessels of the coronary bed. Coronary resistance depends upon the state of vasodilatation or vasoconstriction existing in the coronary bed at the time, and upon the degree of compression exerted on the coronary vessels by the muscular walls of the ventricles.

A typical response of coronary flow to electroshock is seen in Fig. 1, showing that changes in flow follow very closely the changes in arterial pressure, both

in direction and chronology. However, coronary resistance (Table I) decreased from a control value of 4.9 PRU to a value of 3.7 PRU during the hypotensive phase, and increased to 5.3 PRU during the hypertensive phase.

In the perfusion experiments in which the portion of the coronary bed under study was supplied with blood at a constant rate of flow through a pump, the perfusion pressure was independent of changes in arterial pressure. Changes in perfusion pressure thus reflected only changes in coronary resistance; a lowering of perfusion pressure denoted a decrease in resistance, a rise in perfusion pressure, an increase in resistance. Fig. 2 shows a typical record taken from such a preparation. Perfusion pressure fell during the hypotensive phase and then rose above the control level for a brief period while the arterial pressure was rising, and then fell to control levels or below while the arterial pressure was still elevated. Atropine sulfate in dosage of 0.5 mg./Kg. prevented the fall in arterial pressure and the concomitant decrease in perfusion pressure, but did not diminish the rise in perfusion pressure during the hypertensive phase.

Thus, the changes in coronary resistance, whether calculated from the mean arterial pressure and coronary blood flow or measured directly from the experiments on perfusion pressure, were essentially the same, i.e., coronary resistance was decreased during the hypotensive phase and increased during the hypertensive phase. The decrease in coronary resistance, since it is blocked by atropine, is assumed to be vagally mediated. The studies of Schreiner and associates[13] make it appear unlikely that these vagally induced changes are mediated through vasomotor mechanisms. These authors found that stimulating the vagus in the anesthetized dog caused no change either in coronary flow or arterial pressure, provided the heart rate was kept constant by artificial means. It seems more likely that the observed decrease in coronary resistance is due to the mechanical behavior of the heart; during this period the heart spends a greater proportion of its time in diastole and is usually asystolic for several seconds. It is generally accepted in coronary physiology that coronary flow proceeds mainly in diastole, since flow is impeded during systole by the compression of the coronary vessels by the contracting ventricular musculature. This was clearly shown by Sabiston and Gregg[14] in anesthetized dogs. When asystole was produced in these animals by stimulating the vagus or by initiating ventricular fibrillation, an increase in left coronary flow and in coronary sinus drainage invariably occurred.

The increase in coronary resistance is associated with an increased systemic arterial pressure and a more powerful contraction of the ventricles (Table I); both of these latter effects have been shown to be caused by sympathetic discharge following electroshock.[5] It would be expected that the increase in intraventricular pressure resulting from a greater force of ventricular contraction and the increased diastolic arterial pressure would cause the coronary vessels to be compressed to a greater degree, thereby increasing resistance to flow in the coronary bed. In the presence of these marked variations in cardiac muscle tone it is not possible to detect whether coronary vasodilatation or coronary vasoconstriction occurred during the period in which coronary resistance was increasing. The increase in coronary resistance, as shown in the experiments on perfusion, reached its peak and started to decline before the arterial pressure

had attained its highest level; it then returned to the control level or below while the arterial pressure was still considerably elevated. This latter effect is suggestive of a local vasomotor reflex. In anesthetized dogs, Gregg and Shipley[15] determined the effect on left coronary flow of increasing left intraventricular pressure by constricting the aorta centrally to the coronary orifices. When intraventricular pressure was increased gradually, an increase in coronary flow took place almost immediately. When intraventricular pressure was increased abruptly, however, the increase in flow was preceded by a decrease. In both instances, cardiac input and oxygen consumption showed an increase in the work and metabolism of the ventricle. The authors suggest that the increase in flow

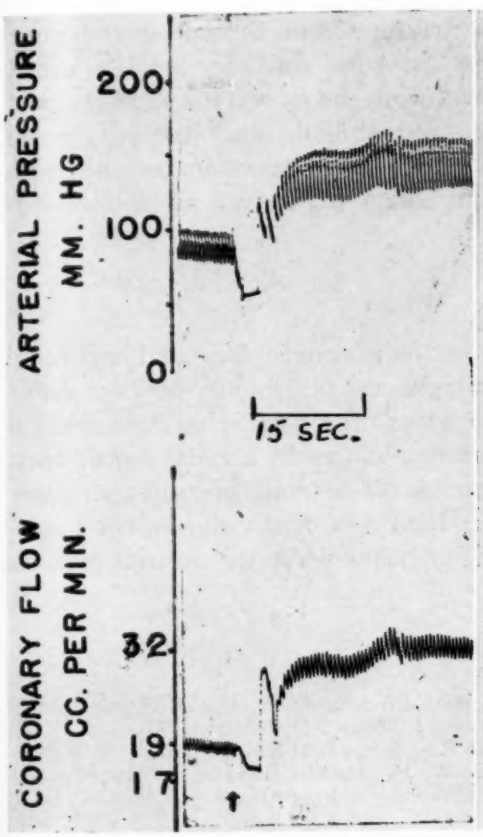

Fig. 1.

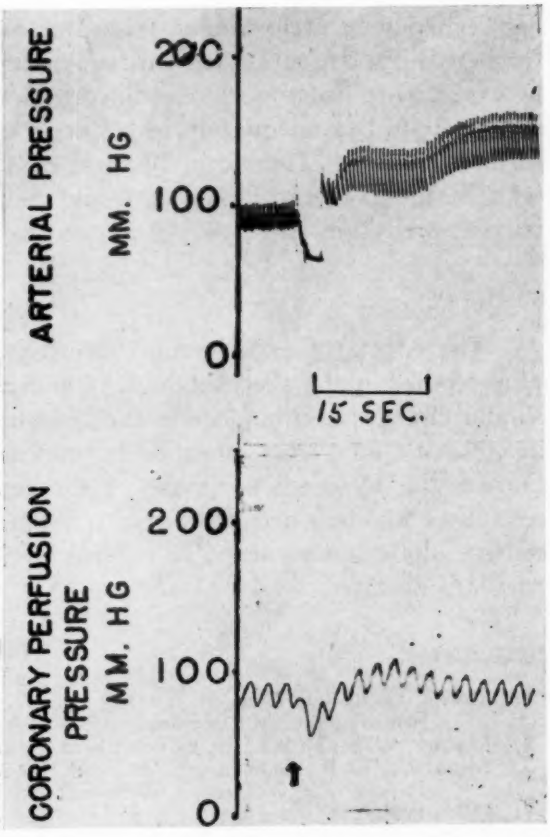

Fig. 2.

Fig. 1.—Stimulus applied at arrow. Changes in systemic arterial pressure and coronary flow induced by electroshock in an anesthetized dog.

Fig. 2.—Stimulus applied at arrow. Changes in systemic arterial pressure and coronary perfusion pressure induced by electroshock in an anesthetized dog.

is due to coronary dilatation in response to the increased cardiac work, the dilatation being brought about either by an increased local production of metabolites or by a local relative anoxia, or by a combination of both of these mechanisms. The temporary decrease in flow when intraventricular pressure was increased

abruptly is interpreted by the authors as being due to a greater compression of the vessels by the elevated ventricular pressure before the slower metabolic reaction causing vasodilatation has an opportunity to act.

In the normal heart there appear to be compensatory mechanisms which act to buffer the coronary circulation from the marked hemodynamic changes induced by electroshock. The initial fall in arterial pressure is accompanied by decreased coronary resistance, because of the fact that the heart spends a greater portion of its time in the diastolic state. Although coronary resistance increases briefly during the hypertensive phase, reflex coronary vasodilatation supervenes to return coronary resistance to control levels or below. The work of Gregg and Shipley suggests that this vasodilatation is in response to an increased cardiac metabolism.

Ventricular arrhythmias following electroconvulsive therapy occur more frequently in patients with cardiac disease. Sclerotic coronary arteries would be expected to exert more resistance to flow during the hypertensive phase, and would dilate less adequately in response to the metabolic stimulus of increased cardiac demand. Therefore, because of failure of compensatory mechanisms, relative anoxia of cardiac tissue would result, which might even precipitate ventricular arrhythmias.

SUMMARY

The effects of experimental electroshock on coronary flow and resistance were studied in anesthetized dogs. In general, changes in coronary flow paralleled similar changes taking place in the systemic arterial pressure. However, changes in coronary flow were modified by concurrent changes in coronary resistance. During the hypotensive phase of the response of arterial pressure, coronary resistance was lessened. Coronary resistance increased briefly during the hypertensive phase but returned to control levels or below while the arterial pressure was still elevated.

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Blood Gas and Plasma Ion Concentrations of Asphyxiated Hypothermic and Normothermic Rats

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It has been established that hypoxia in addition to hypercapnia can effectively aid in lowering the body temperature.[1] Furthermore, a high concentration of carbon dioxide acts as the complement of a cold environment to induce hypothermia.[2] These facts have been utilized in the closed-container technique to facilitate induction of various small mammals into hypothermia with subsequent cardiac arrest. This procedure affords survival after cardiac arrest has been produced and maintained for extended periods of time.[3-6] A complete analysis of the electrocardiogram during one phase of induction into hypothermia and cardiac arrest has shown that the waves of excitation are of decreased frequency and prolonged duration. Recovery from the hypothermic state with cardiac arrest restores the QRS complex to normal frequency and duration.[5] The present study is an attempt to evaluate some of the factors present during induction into hypothermia and cardiac arrest. It is believed that blood analyses for oxygen, carbon dioxide, electrolytes, etc., would give additional insight into some of the factors which contribute to revival and survival of animals from profound hypothermia.

METHODS

Cardiac punctures and blood analyses were made on male hooded rats divided into four experimental groups: hypothermic asphyxiation followed by hypothermia (HAH), ambient asphyxiation followed by hypothermia (AAH), hypothermic asphyxiation (HA), and ambient asphyxiation (AA). Group HAH consisted of 30 animals induced into hypothermia by the closed-container technique of Andjus.[3] After asphyxia the animals were removed from the jar and exposed to further cooling.[5] Rectal temperatures and electrocardiograms were taken periodically until cardiac arrest. When cardiac arrest was obtained, as evidenced by the cessation of electrical activity, an incision was made in the thorax in order to expose the heart. In each case, cardiac punctures were made in the right and left ventricle; the blood was collected in greased, heparinized 10-ml. syringes. Blood samples were analyzed for O_2 and CO_2 by the method of Van Slyke and Neill.[7] The millimolar H_2CO_3 and $BHCO_3$ were calculated by the Henderson-Hasselbalch equation,

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using the pH and pKa after correction for temperature. Plasma K^+ and Na^+ were determined by means of a Beckman model B spectrophotometer with flame attachment. The blood pH was measured on a Cambridge pH meter using a calomel and glass electrode assembly. Hemoglobin was determined spectrophotometrically. Hematocrits were evaluated by a micro-hematocrit technique.

Thirty-one rats in Group HA were subjected to the closed-container technique of inducing hypothermia. Cardiac punctures were made immediately after removal of the animal from the refrigerator. Blood analyses were carried out as previously described.

Group AAH, 14 animals, was exposed to the protocol outlined for Group HAH. During the period of asphyxiation the jar, rather than being placed in a refrigerator, was left in a room at 25°C. Blood analyses were conducted as before.

Group AA consisted of 27 animals that were asphyxiated in a closed jar at an ambient temperature of 25°C. Cardiac punctures for blood analyses were performed immediately.

The animals were under close surveillance to ascertain when comparable levels of hypothermic asphyxiation or normothermic asphyxiation had been attained. Standard statistical procedures were used on all data where warranted, and a significant difference was accepted at the 5 per cent level.

RESULTS

The two groups of animals, HA and HAH, cooled with the closed-container technique, responded similarly during this initial cooling period. They were very restless at first, but within a brief interval appeared to be quiescent and in a stupor; however, when the jar was moved they immediately became active. They were never observed to exhibit any type of convulsion or tonic contraction. Upon removal from the jar they were flaccid and seldom moved except to breathe at a rate of about 3 to 4 per minute. Group HAH occasionally responded when first covered with ice.

The response of the ambient asphyxiated groups of animals was observed to be quite different from that of Groups HA and HAH while in the jar. They remained active throughout most of the period of asphyxiation. Breathing became labored as the animal became more nearly asphyxiated. Just before the animal ceased to breathe the rate of respiration increased rapidly and the animal went into convulsions. Respiration became mostly diaphragmatic, and the animal then passed into a state of unconsciousness. The animals were flaccid and seldom responded when the thoracic cavity was opened.

In Groups HAH and AAH the ventricles were never beating; however, the auricles at times were observed to beat when the thoracic cavity was opened. In both groups, insertion of the needle into the ventricles initiated a beat, which demonstrated that myocardial irritability was still present. Those animals in Groups HAH and AAH which displayed movement when covered with ice resisted cooling, and cardiac and respiratory arrest were obtained at lower temperatures. There was a notable difference in the time necessary to bring about ambient asphyxiation and hypothermic asphyxiation (Table I).

Hematocrits were well within the normal range of 39 to 51 per cent,[8] and did not show any increase as hypothermia progressed. The hemoglobin values remained relatively constant.

Cardiac arrest occurred at 6.2 ± 0.4° C. for Group HAH and 5.4 ± 0.5° C. for Group AAH. These temperatures were somewhat higher than has been reported previously.[5]

In every group except AA, there was a large A-V difference in per cent saturation of hemoglobin. The data confirm that the animals were hypercapnic and anoxemic (Fig. 1). Nevertheless, the tissues were still extracting oxygen from the blood. In addition, oxygen was being delivered to the cells of the body, and carbon dioxide was being removed. In Groups HAH and AAH a significant A-V oxygen difference existed, even after respiratory arrest had existed for several minutes.

Animals in all groups were extremely acidotic, as shown by Table II. In all instances, arterial and venous pH were significantly lower than the normal

TABLE I. SUMMARY OF DATA FROM FOUR GROUPS OF ANIMALS SUBJECTED TO HYPOTHERMIA AND ASPHYXIATION

	HA (MEAN ± S.E.)	AA (MEAN ± S.E.)	HAH (MEAN ± S.E.)	AAH (MEAN ± S.E.)
Time in refrigerator (min.)	132 ± 7	—	126 ± 2	—
Time in jar (min.)	—	89 ± 6	—	74 ± 3
Rectal temperature from refrigerator (°C.)	19.0 ± 0.5	—	19.0 ± 0.5	—
Rectal temperature from jar (°C.)	—	32.2 ± 0.7	—	31.9 ± 0.6
Cardiac arrest (°C.)	—	—	6.2 ± 0.4	5.4 ± 0.5
Hemoglobin (Gm.)				
Venous	11.70 ± 0.41	9.55 ± 0.21	10.67 ± 0.37	9.69 ± 0.25
Arterial	11.95 ± 0.41	9.95 ± 0.39	10.56 ± 0.26	10.40 ± 0.39
Per cent saturation				
Venous	6.8	4.6	10.3	8.3
Arterial	34.2	8.4	36.8	36.6
Weight (Gm.)	285.7 ± 14.6	285.0 ± 13.9	263.5 ± 10.6	329.6 ± 13.8

S. E.: Standard error of the mean. HA: Hypothermic asphyxiation. AA: Ambient asphyxiation. HAH: Hypothermic asphyxiation followed by hypothermia. AAH: Ambient asphyxiation followed by hypothermia.

TABLE II. BLOOD ANALYSIS FROM FOUR GROUPS OF ANIMALS SUBJECTED TO ASPHYXIATION AND/OR HYPOTHERMIA

GROUP	pH[9]	pKa[10]	mM.CO_2/100 ML. BLOOD	pCO_2(MM.Hg)	mM.H_2CO_3/100 ML. BLOOD	mM.$BHCO_3$/100 ML. BLOOD
			Arterial			
HA	7.11 ± 0.03	6.21	29.95 ± 2.00	111.8	3.35	26.60
AA	6.75 ± 0.05	6.15	16.80 ± 1.22	112.8	3.38	13.42
HAH	7.15 ± 0.04	6.28	24.50 ± 1.50	96.8	2.90	21.60
AAH	7.11 ± 0.03	6.29	15.83 ± 1.29	69.4	2.08	13.75
			Venous			
HA	7.01 ± 0.05	6.22	26.98 ± 1.35	125.5	3.77	23.21
AA	6.64 ± 0.05	6.16	23.03 ± 0.42	190.2	5.70	17.32
HAH	7.15 ± 0.02	6.28	30.44 ± 1.15	120.3	3.60	26.84
AAH	6.61 ± 0.05	6.35	17.25 ± 0.68	202.9	6.09	11.16

HA: Hypothermic asphyxiation. AA: Ambient asphyxiation. HAH: Hypothermic asphyxiation followed by hypothermia. AAH: Ambient asphyxiation followed by hypothermia.

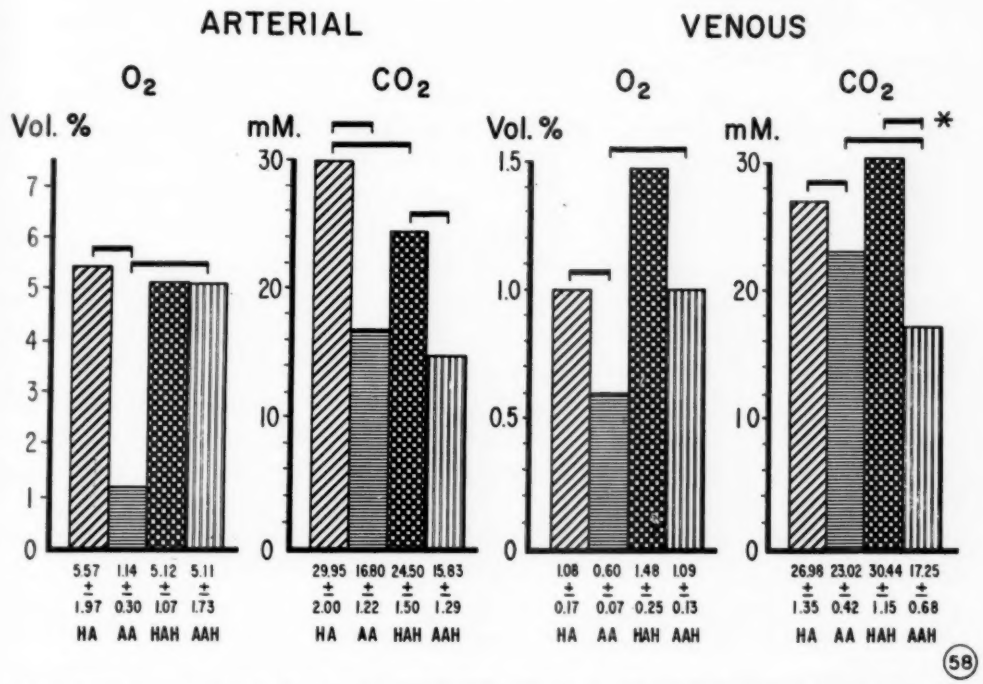

Fig. 1.—Concentrations of carbon dioxide and oxygen in arterial and venous blood obtained by cardiac punctures in four groups of rats. $P \leq 0.05$ (*). Hypothermic asphyxiation (*HA*). Ambient asphyxiation (*AA*). Hypothermic asphyxiation followed by hypothermia (*HAH*). Ambient asphyxiation followed by hypothermia (*AAH*).

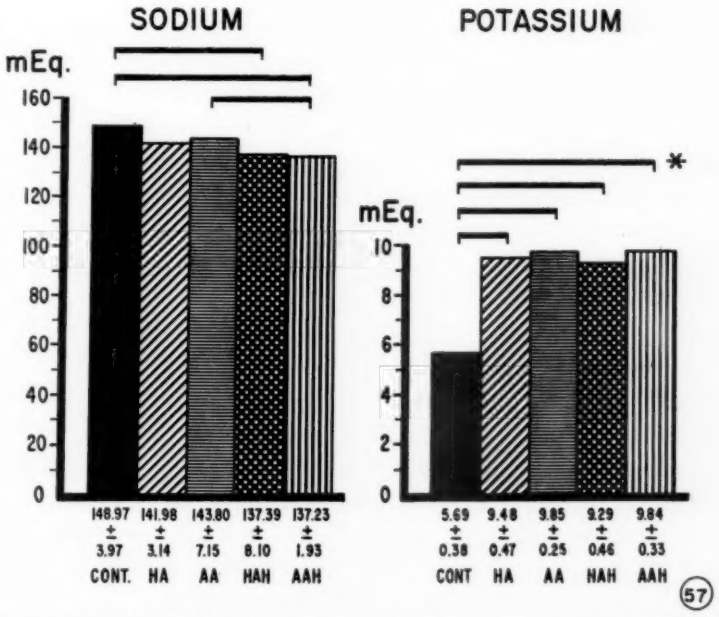

Fig. 2.—Concentrations of Na^+ and K^+ in the blood from four groups of animals. $P \leq 0.05$ (*). Control (*cont*). Hypothermic asphyxiation (*HA*). Ambient asphyxiation (*AA*). Hypothermic asphyxiation followed by hypothermia (*HAH*). Ambient asphyxiation followed by hypothermia (*AAH*).

range of 7.35 to 7.45. The $BHCO_3/H_2CO_3$ ratio indicates a decreased buffering capacity of the blood, especially in those groups asphyxiated ambiently. The tissue cells lost K^+ and gained in Na^+ (Fig. 2). There was an increase of at least 80 per cent in plasma potassium in all cases. However, only Groups HA and HAH exhibited a significant decrease in plasma sodium from control values.

DISCUSSION

The time differences in inducing ambient asphyxiation and hypothermic asphyxiation (Table I) can be explained, in part, by a consideration of the size of the animals in the various groups in relation to the amount of oxygen available to them. Even more important though, the time differential probably was related to the fact that hypothermia and excessive amounts of carbon dioxide act as complements to depress oxidative metabolism. Thus, in the hypothermic asphyxiated groups the oxygen was consumed more slowly and the animal took a longer time to become comatose.

Considerable interest exists as to whether the cells of the body are functioning metabolically, and to what extent during profound hypothermia.[3-6] The data from this study suggest that oxidative processes were taking place even at the time of cardiac arrest. As suggested by the A-V oxygen and carbon-dioxide differences, exchange of both oxygen and carbon dioxide occurred at both the alveolar and tissue level. Whether sufficient oxygen was available to the tissues cannot be determined from the present data. Even though the A-V oxygen differences appear approximately in a proper proportion, the absolute amounts of oxygen were low. Adolph[11] has found a zero A-V difference at the time of cardiac arrest; in the present experiments, however, an A-V difference in the concentration of the gases existed in all cases, which indicated that oxygen was being extracted at the time of cardiac arrest. If the animal were allowed to remain in cardiac arrest for a substantial length of time before cardiac punctures were performed, the A-V differences would possibly have approached zero. Since cardiac arrest occurred considerably later than respiratory arrest, it appears that the body has to depend upon the oxygen stores, such as the lungs, oxyhemoglobin, dissolved plasma oxygen, etc., for its supply of oxygen. The amount of oxygen used below 15° C. was small, and the rate of utilization was probably an important factor in determining survival, especially in relation to the duration of cardiac arrest.

The success of reviving hypothermic animals has been related by some investigators to the acidity of the body fluids.[12,13] In all the present groups the pH was significantly lower than normal values. The acidosis observed, however, was not due to the accumulation of carbon dioxide, but to the diminution of the alkaline reserve by acid metabolites. The ratio of $BHCO_3$ to H_2CO_3 was quite small in all cases and particularly so in those groups asphyxiated ambiently. The lower $BHCO_3$ levels suggested lesser buffering capacity of the blood in Groups AA and AAH. Thus, if the lower pH was due to a metabolic acidosis consequent to a higher metabolic rate, the increased consumption of oxygen by animals asphyxiated ambiently could be related to nonsurvival, since if anoxic conditions existed, resuscitation would be difficult to obtain.[14] This relationship between

consumption of oxygen, pH and levels of carbon dioxide illustrates the complexity of evaluating the survival of animals induced into hypothermia. Apparently the lowered pH has little effect on the heart, for, contrary to observations on dogs, no fibrillation has been observed in animals induced into hypothermia by the closed-container technique. This may be related to species variation or the size of the rat heart in relation to the size of the canine heart. An additional inference would be that the rat, when induced into hypothermia by the closed-container technique, may offset the response to a lowered pH by some "conditioning." This conditioning may be the attainment of greater amounts of $BHCO_3$ during the early part of the induction procedure when the metabolism of the animal is greatest, or by a depression of the oxygen consumption by high concentration of carbon dioxide.

The effect of cold and carbon dioxide on the metabolism is exemplified by the change in concentrations of intra- and extracellular Na^+ and K^+. According to the ionic theory, Na^+, K^+, and Cl^- are maintained in the definite intra- and extracellular ratios by some active process via the "sodium pump." A discussion of this theory is beyond the scope of this article; however, it is proper to assume that oxygen is utilized over various enzyme systems for the maintenance of the electrolyte ratios. Thus, the concentrations of electrolytes can be altered by either a lack of oxygen or a depression of the enzyme kinetics. It has already been suggested that cellular anoxia does not exist; so the remaining alternative, i.e., depression of enzyme activity, apparently is responsible. The depression of the enzyme kinetics could be brought about by lowered temperature of tissue or decreased pH. If, however, the depression were due to pH, irreversible damage to the organism should result. Since these animals can be revived and a large number survive without any difficulty, it can be concluded that the change in electrolyte concentrations resulted from a depression of the enzymatic reactions subsequent to cold. The change in electrolytes can be used in part to explain the decreased and prolonged action potential during electrical systole. Since a decreased resting potential results from the change in electrolytes, when electrical systole takes place, an altered action potential would result.

The depression of enzyme kinetics may not have been the only reason for the change in intra- and extracellular electrolyte concentrations. Certainly some trauma, i.e., peripheral frostbite, takes place. The cells were undoubtedly ruptured and electrolytes were released. However, freezing of the peripheral tissues was not extensive; so it is assumed that the major portion of the electrolyte shifts was due to the depressant effect of cold on the enzymes.

It has been proposed that asphyxiation combined with hypothermia conditions an animal for deep hypothermia from which survival can be expected. It has been shown that oxygen is being utilized, a lowered blood plasma pH results, and alterations in blood plasma electrolytes occur during progressive hypothermia. What then is the limiting factor in producing deep hypothermia with cardiac arrest? Since pH and the electrolyte shifts cause no apparent irreversible damage, the limiting factor for successful revival of animals from deep hypothermia is probably the amount of oxygen available. After cardiac arrest or after cessation of body fluid movement the demand of the tissues for oxygen

will have to be supplied by the body stores alone. The evaluation of this factor needs further investigation.

SUMMARY

1. Cardiac punctures were made in four groups of rats during and after the time they were subjected to the procedures described for the induction of hypothermia with subsequent cardiac arrest.

2. The absolute amounts of oxygen were low and the carbon dioxide was high in the arterial and mixed venous blood. Even under these situations a large A-V oxygen and carbon-dioxide difference remained.

3. Although animals in all groups were acidotic, fibrillation was not observed on the electrocardiographic recordings during immersion of the animals of Groups AAH (ambient asphyxiation followed by hypothermia) and HAH (hypothermic asphyxiation followed by hypothermia) in the ice baths.

4. A decreased buffering capacity of the blood, as evidenced by the $BHCO_3/H_2CO_3$ ratio, was prominent especially in those groups ambiently asphyxiated.

5. Plasma K^+ increased at least 80 per cent in all groups. However, plasma sodium exhibited a significant decrease only in Groups HA (hypothermic asphyxiation) and HAH.

6. It is suggested that one of the limiting factors for the induction of hypothermia with cardiac arrest is the absolute amount of oxygen available to the animal after respiratory arrest.

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Electrocardiographic Cancellation: Mathematical Basis

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It is the purpose of this paper to investigate the mathematical basis underlying electrocardiographic cancellation and to generalize the entire concept in order that it might be applied to the investigation of equivalent heart generators of greater complexity than that of a single, stationary dipole. Application of the cancellation technique has been restricted previously to study of the latter type of equivalent generator.[1-6]

It was shown several years ago[7] that

$$\text{lead x} = (1 - q_1 - q_2 - \ldots - q_{(n-1)})\text{lead 1} + q_1\text{lead 2} + q_2\text{lead 3} + \ldots + q_{(n-1)}\text{lead n} \quad (1)$$

where lead x is a synthetic lead formed by the addition of n leads, each of which is multiplied by its respective coefficient. This equation can be written in a more convenient form as

$$P = Q_1L_1 + Q_2L_2 + Q_3L_3 + \ldots + Q_nL_n \quad (2)$$

in which lead x is replaced by P, each of the n leads is replaced by the symbol, L, further designated by a subscript, and each of the coefficients is replaced by the symbol, Q, possessing a subscript identical to the subscript of the corresponding L term. Equations (1) and (2) are generalizations of the equation, lead = aX + bY + cZ, published in 1946, by Burger and van Milaan[8] for the synthesis of a lead from three leads rather than from n leads.

In the application of the cancellation technique, the time-varying potentials of an actual lead and the time-varying potentials of a synthetic lead are recorded simultaneously. The quantity, P, of Equation (2) represents one instantaneous potential of such a synthetic lead. The L terms of Equation (2) represent simultaneous, instantaneous potentials of the n leads which are summated to form the synthetic lead. Therefore, both P and the L terms vary continually with time. The Q terms, however, do not vary with time. Let the potential of the actual lead be represented at any instant by P′. When the polarities of the actual and synthetic leads have opposite signs, the equation,

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$$R = P' - P, \tag{3}$$

may be written in which R is the residual instantaneous voltage resulting from the subtraction. All three terms of Equation (3) vary with time. Perfect cancellation requires that R = 0 at all instants of the cardiac cycle or at all instants of any specified portion of the cycle, for example, the period of inscription of the QRS complex. Any positive or negative values of R represent deviations from perfect cancellation.

In the usual application of the cancellation technique,[1-6] the maximum peak-to-nadir spread or range* of the values of R plotted against time is measured when such a range is adjusted to be a minimum by the selection of optimal Q coefficients. The minimum range method of cancellation is useful because it is practical for monitoring the selection of Q coefficients by means of a time-varying cathode-ray beam.

A second method of evaluating a cancellation pattern consists of summating the squares of each of the instantaneous deviations of R from zero when the Q coefficients are so selected to reduce such a sum of squares to its minimum value. The root mean square deviation from zero can then be extracted. The minimum root mean square cancellation cannot be applied to monitoring the selection of Q coefficients with a cathode-ray oscilloscope unless the data are first analyzed by an electronic computer. It can be computed, however, when cancellations are applied to data calculated from a mathematical model or obtained from a physical model of the human body.

MINIMUM ROOT MEAN SQUARE CANCELLATION

The mathematical basis for minimizing the root mean square of the deviations from zero of a cancellation pattern will be considered first. By substituting the right-hand terms of Equation (2) for P in Equation (3), the following equation is obtained:

$$R = P' - (Q_1L_1 + Q_2L_2 + Q_3L_3 + \ldots + Q_nL_n). \tag{4}$$

Squaring each side of Equation (4) and summating all values of R^2 at each of t specified instants of time,

$$\begin{aligned}\Sigma R^2 = {} & \Sigma(P')^2 - 2Q_1\Sigma(P'L_1) - 2Q_2\Sigma(P'L_2) - 2Q_3\Sigma(P'L_3) - \ldots \\ & - 2Q_n\Sigma(P'L_n) + Q_1^2\Sigma L_1^2 + Q_2^2\Sigma L_2^2 + Q_3^2\Sigma L_3^2 + \ldots + Q_n^2\Sigma L_n^2 \\ & + 2Q_1Q_2\Sigma(L_1L_2) + 2Q_1Q_3\Sigma(L_1L_3) + \ldots + 2Q_1Q_n\Sigma(L_1L_n) \\ & + 2Q_2Q_3\Sigma(L_2L_3) + \ldots + 2Q_2Q_n\Sigma(L_2L_n) + 2Q_3Q_4\Sigma(L_3L_4) \\ & + \ldots + 2Q_3Q_n\Sigma(L_3L_n) + \ldots + 2Q_{(n-1)}Q_n\Sigma(L_{(n-1)}L_n).\end{aligned} \tag{5}$$

In order to calculate the Q coefficients which will yield the smallest value for ΣR^2, Equation (5) can be partially differentiated n times to obtain n simultaneous equations. Only the first two and the last of this series of partial derivatives will be written:

$$\begin{aligned}\frac{\partial \Sigma R^2}{\partial Q_1} = {} & -2\Sigma(P'L_1) + 2Q_1\Sigma L_1^2 + 2Q_2\Sigma(L_1L_2) + 2Q_3\Sigma(L_1L_3) + \\ & \ldots + 2Q_n\Sigma(L_1L_n) = 0,\end{aligned} \tag{6-1}$$

*The term "range" will henceforth be used in its statistical sense to indicate the maximum spread of positive and negative potential points.

$$\frac{\partial \Sigma R^2}{\partial Q_2} = -2\Sigma(P'L_2) + 2Q_1\Sigma(L_1L_2) + 2Q_2\Sigma L_2^2 + 2Q_3\Sigma(L_2L_3) + \ldots + 2Q_n\Sigma(L_2L_n) = 0, \quad (6\text{-}2)$$

$$\ldots = \ldots = 0, \quad (6\text{-}x)$$

$$\frac{\partial \Sigma R^2}{\partial Q_n} = -2\Sigma(P'L_n) + 2Q_1\Sigma(L_1L_n) + 2Q_2\Sigma(L_2L_n) + 2Q_3\Sigma(L_3L_n) + \ldots + 2Q_n\Sigma L_n^2 = 0. \quad (6\text{-}n)$$

Since, in the case of a cancellation experiment on a model, the instantaneous values of P' and of L_1, L_2, L_3, . . . and L_n at the t specified time intervals may be calculated or measured, these quantities can be substituted in the n simultaneous equations, and the values of Q_1, Q_2, Q_3, . . . and Q_n may be computed. If these coefficients are substituted in Equation (5), ΣR^2 can be calculated. The value of ΣR^2 will be the smallest obtainable; no other combination of Q coefficients would yield a smaller value. ΣR^2 can then be divided by t, and the square root of the quotient extracted to yield the value of the root mean square deviation from zero. The Q coefficients likewise may be substituted in Equation (4), and the value of R at each specified instant of time may be calculated. From such data the variable, R, can be plotted against time to display the cancellation pattern graphically.

The minimum root mean squares of two cancellation patterns involving different actual leads cannot be compared without considering the magnitudes of the root mean squares of the deviations from zero of the actual leads. If an actual lead shows relatively small deflections, it is likely that its cancellation pattern would show smaller deflections than a cancellation pattern involving an actual lead possessing relatively large deflections. A coefficient, C_s, expressing the cancellation in per cent is

$$C_s = 100\sqrt{\Sigma R^2/\Sigma(P')^2}. \quad (7)$$

This coefficient is a convenient one for comparing cancellations. The coefficient, C_s, may also be squared for variance analysis if a statistical study is to be carried out. It should be emphasized that any ratio similar to C_s for expressing a coefficient of cancellation should not contain the sum of squares, ΣP^2, of the synthetic lead in its denominator. If the synthetic lead partially determines the denominator, the resulting ratio might not possess a minimum value with the Q coefficients computed with Equations (6), since such Q coefficients, which yield a minimum numerator, would also affect the term representing the synthetic lead in the denominator.

MINIMUM RANGE CANCELLATION

The range of the instantaneous potentials of a cancellation pattern may be minimized by proper selection of the Q coefficients to be substituted in Equation (4) for the calculation of R at each specified instant of time. To develop a method of attacking this problem, let the symbol, S, represent the difference in potential between two values of R. If there are t instants of time, t(t-1), separate equations may be written:

$S_{1,2} = R_1 - R_2$	(8-1,2)	$S_{2,1} = R_2 - R_1$	(8-2,1)
$S_{1,3} = R_1 - R_3$	(8-1,3)	$S_{3,1} = R_3 - R_1$	(8-3,1)
$\ldots = \ldots$	(8-1,x)	$\ldots = \ldots$	(8-x,1)
$S_{1,t} = R_1 - R_t$	(8-1,t)	$S_{t,1} = R_t - R_1$	(8-t,1)
$S_{2,3} = R_2 - R_3$	(8-2,3)	$S_{3,2} = R_3 - R_2$	(8-3,2)
$\ldots = \ldots$	(8-2,x)	$\ldots = \ldots$	(8-x,2)
$S_{2,t} = R_2 - R_t$	(8-2,t)	$S_{t,2} = R_t - R_2$	(8-t,2)
$\ldots = \ldots$	(8-3,x)	$\ldots = \ldots$	(8-x,3)
$S_{3,t} = R_3 - R_t$	(8-3,t)	$S_{t,3} = R_t - R_3$	(8-t,3)
$\ldots = \ldots$	(8-x,x)	$\ldots = \ldots$	(8-x,x)
$S_{(t-1),t} = R_{(t-1)} - R_t$	(8-(t-1),t)	$S_{t,(t-1)} = R_t - R_{(t-1)}$	[8-t,(t-1)]

If a cancellation pattern is formed by either all-positive or all-negative potential points (see example in Table II under the Discussion), the zero end points constitute the lower and upper range limits, respectively, of the graph. It is necessary, therefore, to include 2t additional equations of the following form:

$S_{0,1} = -R_1$	(8-0,1)	$S_{1,0} = R_1$	(8-1,0)
$S_{0,2} = -R_2$	(8-0,2)	$S_{2,0} = R_2$	(8-2,0)
$\ldots = \ldots$	(8-0,x)	$\ldots = \ldots$	(8-x,0)
$S_{0,t} = -R_t$	(8-0,t)	$S_{t,0} = R_t$	(8-t,0)

These 2t equations bring the total number to $t(t + 1)$.

In the following discussion, let the signs of the various S quantities of Equations (8) be disregarded, that is, let $|S| = \pm S$. Consider first a special case of Equation (4) in which n is 1, that is, $R = P' - Q_1L_1$. Let *any* $|S|$, for example, $|S_{k1}|$, represent the range of the instantaneous potentials of the cancellation pattern as the result of the selection of a certain value for Q_1. By either progressively reducing or increasing Q_1, $|S_{k1}|$ can be made progressively smaller. However, $|S_{k1}|$ will continue to have the largest peak-to-nadir spread on the cancellation graph until *any other* $|S|$, for example, $|S_{k2}|$, develops a greater peak-to-nadir spread as the result of the unidirectional change in Q_1. Therefore, that value of Q_1 which permits $|S_{k1}|$ to equal $|S_{k2}|$ will yield a value for $|S_{k1}|$ and $|S_{k2}|$ which is as large as, or usually larger than, the value of *any* remaining $|S|$. At the same time, such a value of Q_1 compresses the cancellation pattern into a graph which has the smallest possible range of potentials. This is the value of Q_1 which is sought.

In connection with Equations (8), consider a second special case of Equation (4) in which n is 2, that is, $R = P' - Q_1L_1 - Q_2L_2$. Let *any* $|S|$, for example, $|S_{k1}|$, represent the range of the cancellation potentials as the result of the selection of certain values for Q_1 and Q_2. If Q_2 is held constant, Q_1 may be either reduced or increased progressively to bring about a progressive diminution in $|S_{k1}|$. However, $|S_{k1}|$ will continue to have the greatest peak-to-nadir spread on the cancellation graph until *any other* $|S|$, for example, $|S_{k2}|$, develops a larger peak-to-nadir spread. Therefore, with Q_2 constant, that value of Q_1 which permits $|S_{k1}|$ to equal $|S_{k2}|$ will yield a value for $|S_{k1}|$ and $|S_{k2}|$ which is as large as, or larger than, the value of any remaining $|S|$. If Q_1 and Q_2 are then varied simultaneously in such a manner that $|S_{k1}|$ and $|S_{k2}|$ diminish but remain equal, the cancellation graph will have the smallest possible range when Q_1 and Q_2 have such values that another $|S|$, for example, $|S_{k3}|$, increases to the point at which $|S_{k1}| = |S_{k2}| = |S_{k3}|$.

In a similar manner it may be shown that for any number of leads, n, in Equation (4) it is possible, by suitable manipulation of the n available Q coefficients, to obtain $(n+1)$ *equal* values from the array of $|S|$ quantities available by virtue of Equations (8). Moreover, if the $(n+1)$ equal $|S|$ values are obtained as the result of the manipulation of the n available Q coefficients in the systematic manner described, these $|S|$ values will be as large as, or usually larger than, any other $|S|$ value and, at the same time, will represent the smallest possible peak-to-nadir spread of the cancellation graph. Such a minimum range could not be further reduced by the slightest change or changes in one or more of the Q coefficients.

The foregoing description of the systematic method of selecting Q coefficients is applicable to the monitoring of minimum range patterns on an oscilloscope. In the calculation of such cancellations from data on models, a basically similar approach is available which may be outlined systematically as follows:

1. If there are t specified instants of time at which potentials are calculated or measured, there are $t(t+1)$ separate equations of the form given in Equations (8). The latter should be tabulated systematically and the right-hand member of Equation (4) should be substituted for the R quantities.

2. If there are n leads available for synthesizing the synthetic lead, the number of $|S|$ quantities which will be equal when the synthetic lead produces the minimum range cancellation pattern is $(n+1)$. The $t(t+1)$ equations tabulated in Step 1 should be grouped systematically into all possible combinations, of which there are $\frac{[t(t+1)]!}{[n+1]!\,[t(t+1)-(n+1)]!}$, each group containing $(n+1)$ equations.

3. Since all of the $|S|$ terms of the $(n+1)$ equations in each group are equal, these terms can be eliminated to form n independent equations for each group. The Q quantities, of which there are n in each group, can then be computed from these n simultaneous equations.

4. After the Q quantities for each group have been determined, $|S|$ is calculated for each group. These groups are then arranged in the order of their increasing $|S|$ values.

5. The Q quantities of that group possessing the smallest calculated $|S|$ are substituted in Equation (4) to determine the potential of R at each of the specified instants of time. These t values of R are then inspected to determine their range.* If the range is greater than the calculated $|S|$ for that group, the process is repeated with the group having the next larger calculated $|S|$. If again the range of the R potentials* exceeds this $|S|$, the process is repeated serially in like manner until a group is found in which the calculated $|S|$ forms the range limits. There is then no further need to subject groups possessing larger calculated $|S|$ values to this process.

6. In most instances the last group analyzed in Step 5 provides the Q quantities, calculated in Step 3, which uniquely determine the minimum range can-

*If all of the R values are either positive or negative, the zero end points constitute one of the range limits.

cellation pattern. However, in special circumstances, two groups may have the same value of $|S|$, calculated in Step 4. Both of these groups should be subjected to Step 5 to obtain two cancellation patterns with the same minimum range (see example in Table II). Moreover, the ranges of the R potentials of all groups analyzed serially in Step 5 should be tabulated. It is theoretically possible for two or more of these ranges to be both equivalent and minimal. Thus, cancellation patterns with different configurations but with the same minimum range may exist (see example in Table II). However, it is impossible for the range of the R potentials of any group to be smaller than the range obtained with the last group analyzed in Step 5, in which the range is identical with the value of $|S|$, calculated in Step 4. Consequently, such a tabulation of the ranges of the R potentials of all groups provides a partial check of the total computation.

Since, as noted in Step 2, there are $\frac{[t(t+1)]!}{[n+1]!\ [t(t+1)-(n+1)]!}$ groups of $(n+1)$ simultaneous equations, the application of the foregoing method is a formidable task even when t and n are relatively small. (It should be pointed out that t must always exceed n by at least 2, so as to permit calculation of the minimum range cancellation.) The method is, however, both general and systematic and is well adapted to solution with an electronic computer. If a desk calculator is to be used, certain characteristics of minimum range cancellations provide a partially intuitive approach which frequently leads to a considerably abbreviated method of solution. This approach will be described under the Discussion.

In expressing the result of a minimum range cancellation, it has been suggested that the range of the cancellation pattern be divided by the arithmetic mean of the range of the actual lead pattern and the range of the synthetic lead pattern.[6] This quotient is multiplied by 100 in order to express the result in per cent. However, the Q coefficients which are calculated by the method described herein, and which yield the smallest possible numerator in such an expression, also determine the pattern of the synthetic lead which partially determines the value of the denominator. It is, therefore, theoretically possible that the smallest numerator, which is the desired quantity, may not always yield the smallest value calculated by this ratio and expressed in percentage.* For this reason, it should be emphasized that the best expression of the result of the cancellation is the ratio of the range of the cancellation pattern to the range of the actual lead pattern multiplied by 100. Such a coefficient may be represented by the symbol, C_r.

Equation (2) is in a form which is most convenient for carrying out the various computations described in the foregoing sections. It may also be written as

$$P = Q(q_1L_1 + q_2L_2 + q_3L_3 + \ldots + q_nL_n) \qquad (2a)$$

where $Qq_1 = Q_1$, $Qq_2 = Q_2$, $Qq_3 = Q_3$, ... and $Qq_n = Q_n$.

In describing the characteristics of a synthetic lead, Equation (2a) is preferable to Equation (2), since Q (capital letter), the coefficient which determines the magnitude of the lead, may be partitioned from the q (lower-case letter) quantities which collectively determine its direction. Equations (2) and (2a) are readily interchangeable, since, in all instances, $q_1 + q_2 + q_3 + \ldots + q_n = 1$.

*An example given in Table I under the Discussion illustrates this possibility.

DISCUSSION

The cancellation technique heretofore has been applied only to the study of problems involving the hypothesis of a single, fixed-location, variable-moment dipole as an equivalent heart generator. Therefore, there has been no necessity for the number of leads involved in the formation of the synthetic lead to exceed three. However, it is becoming increasingly apparent that a single dipole of fixed location may be an inadequate representation of the heart. If more complicated equivalent heart generators are postulated, for example, a single dipole of variable location or multiple dipoles of constant location, the cancellation technique[9,10] can be applied more effectively to their study if the number of leads forming the synthetic lead is unlimited. This communication described the mathematical methods for handling an unlimited number of leads.

The detailed mathematical analysis of the minimum range cancellation brings to light certain characteristics of this type of pattern. If n leads enter into the formation of the synthetic lead, the cancellation will contain $(n + 1)$ equal values of the largest $|S|$. The graph of the cancellation will, therefore, have $(n + 2)$ instantaneous potentials forming the critical points which determine the upper and lower range limits of the cancellation graph. Of these $(n + 2)$ potentials, those which have a positive value are equal and those which have a negative value are equal. Therefore, in any minimum range cancellation, the upper limit of the graph may be formed by 1 to $(n + 1)$ critical points, and if there is more than one point, all are equal. If the number of critical points forming the upper limit of the graph is designated by the symbol, m, the number of critical points forming the lower limit of the graph is $(n + 2)$-m, and if there is more than one point, all are equal. If a minimum range cancellation consists entirely of either positive or negative potentials, the respective upper or lower limit of the graph is formed by $(n + 1)$ equal points, and the respective lower or upper limit is formed by the zero end points.

The equality of the m limiting upper points and the equality of the $(n+2)$-m limiting lower points cannot be appreciated in cancellations recorded with an oscillograph, because the total number of points forming the graph at all instants of time is infinite. Thus, two equal potential points may be so close to each other in time that they cannot be visualized as separate points. However, in graphs which are calculated for t instants of time, the critical points forming the upper limit of the graph should have the same potential, and likewise those forming the lower limit of the graph should be equal. If $n = 3$, that is, if three leads are used to form the synthetic lead, the number of critical limiting points is 5. These could be distributed as 3 equal limiting points above the isoelectric line and 2 equal limiting points below the line, or vice versa, as 4 equal limiting points above the isoelectric line and 1 limiting point below the line, or vice versa, or as only 4 equal limiting points either above or below the isoelectric line, with the additional proviso that all other potential points would be located on the same side of the isoelectric line. Careful examination of the graphs published in the recent paper of McFee and Parungao[11] indicate that none of these criteria are met. This means that their cancellation patterns do not have the smallest

peak-to-nadir spread which could be achieved if the systematic method described herein for obtaining a minimum range cancellation were applied to their data.

Consideration of the fact that a minimum range cancellation pattern has (n + 2) instantaneous potential points determining its range limits suggests a simplified method of computing such a graph. Since the patterns of a minimum range and a minimum root mean square cancellation are quantitatively similar, particularly with regard to the times of occurrence of peaks, nadirs, and zero crossing points, the latter type of cancellation is calculated initially. If n is not too large, such a computation may be easily carried out with a desk calculator, regardless of the value of t. Inspection of the resulting graph can then be utilized for the intuitive selection of m likely limiting positive points and (n + 2)-m likely limiting negative potential points. If m exceeds 1, the selected upper R potential points are set as equal, and if m is less than (n + 1), the selected lower R potential points are set as equal. From these one or usually two sets of equivalent R potentials it is always possible to form n independent and simultaneous equations. Substitution of the right-hand member of Equation (4) for each of the instantaneous R potentials leads to the calculation of the n coefficients, Q_1, Q_2, Q_3, . . . and Q_n, which determine the cancellation pattern. If any R potential is more positive than the m selected and equalized positive potential points, or more negative than the (n + 2)-m selected and equalized negative potential points, the cancellation does not have a minimum range. The entire process then must be repeated by selecting and equalizing other combinations of m positive potential points and (n + 2)-m negative potential points until the points selected form the range limits of the resulting graph. Even such a finding does not preclude the possibility that the range has not been minimized. However, further intuitive selection and testing of other combinations of points will usually bring reasonable assurance that the minimum range cancellation has been achieved.

Morton, Romans and Brody[5] have correctly indicated that the deflections of a lead at any two given instants during the cardiac cycle can always be cancelled completely. In reality, the number of points on the graph produced by an actual lead which can always be completely cancelled, that is, brought to the isoelectric line, by a synthetic lead depends upon the number of leads forming the synthetic lead. If this number is n, a synthetic lead can be produced which will yield a cancellation pattern having zero potential at n separate instants of time rather than at only two. Proof of this is provided by Equation (4). If there are n leads, it is possible to set R = 0 at n different instants of time. There are then n simultaneous equations available for obtaining the n coefficients, Q_1, Q_2, Q_3, . . . and Q_n.

Morton, Romans and Brody[5] also state: "In the case of a diphasic complex the conditions can be arbitrarily chosen to produce complete cancellation of the maximum positive and negative potentials. Therefore, without regard to the equivalent cardiac dipole hypothesis, complete cancellation of the major peaks of a diphasic esophageal QRS complex is assured a priori." This statement is undoubtedly true from the considerations in the last paragraph. However, it should be emphasized that *complete* cancellation of the two major peaks (i.e., major peak and major nadir) of a diphasic pattern does not lead to the minimum

range cancellation pattern nor to the minimum root mean square cancellation pattern. The data listed in Table I have been selected to illustrate these facts. At each of 6 instants of time, the arbitrarily chosen potentials of a lead to be cancelled are listed in the column under P′. Three leads, L_1, L_2, and L_3, have been selected to produce the synthetic lead, and their arbitrary potentials are listed for each instant of time. Three synthetic leads have been formed which are designated as P_o, P_r, and P_s, respectively. P_o represents one synthetic lead which produces complete cancellation of the maximum positive and negative potentials of P′. There are an infinite number of such leads which could be formed, since only 2 points are being completely cancelled by a synthetic lead formed by 3 leads. However, lead P_o has the additional characteristic that, when the maximum and minimum potentials of P′ are completely cancelled, the cancellation of the four remaining potentials yields the smallest possible peak-to-nadir spread. (The method of computing this result will not be given, since it is not germane to the discussion.) P_r represents the synthetic lead which produces the minimum range cancellation pattern for all six potentials of P′. P_s represents the synthetic lead which produces a cancellation in such a manner that the sum of squares of its six deviations from zero is a minimum. Both P_r and P_s are obtained by the methods described in this communication. The coefficient of magnitude, Q, and the coefficients of direction, q_1, q_2, and q_3, which, from Equation (2a), yield the leads, P_o, P_r, and P_s, are listed in their respective columns in Table I. Finally, the values of the potentials of the respective cancellation patterns—$R_o = P' - P_o$ representing the minimum peak-to-nadir cancellation consistent with zero deflection at the .02 and .05 second instants of time; $R_r = P' - P_r$ representing the minimum range cancellation; and $R_s = P' - P_s$ representing the minimum root mean square cancellation—are listed under their respective headings. It is seen that the R_r cancellation has 3 equal potentials for its upper limit and 3 equal potentials for its lower limit. In accordance with theory, only $(n + 2)$ or 5 limiting points are expected. The location of all 6 points at the upper and lower limits results from the arbitrarily chosen symmetry both of lead P and of the combined leads L_1, L_2, and L_3. This is, therefore, a special case which does not invalidate the general theory. It is also evident that the cancellation patterns, R_r and R_s, each cross the isoelectric line at only one point, which is located between .03 and .04 second. It is realized that optimal cancellation patterns of either type usually cross the base line at several instants of time, but this particular example was chosen to demonstrate that optimal cancellation may theoretically occur with only one crossing point.

The ratio of the range of the cancellation pattern to the range of the actual lead pattern is expressed as C_r. This coefficient is 60 per cent for the cancellation pattern in which the maximum positive point at .02 second and the maximum negative point at .05 second of the actual lead are brought to the zero line; it is only 50 per cent for the minimum range cancellation. The latter cancellation erroneously appears to be inferior, however, if ratios involving the use of P in the denominator are used. These are given as $100R/\frac{1}{2}(P' + P)$, an expression used by Okada, Langner and Briller,[6] and as $50R(1/P' + 1/P)$, a formula advocated by Morton, Romans and Brody.[5] Thus, this numerical example supports the suggestion given in the previous section that the simple ratio of the range of

TABLE I (SEE TEXT)

TIME (t) IN SECONDS	POTENTIALS IN ARBITRARY UNITS									
	P'	L_1	L_2	L_3	P_o	$R_o = P' - P_o$	P_r	$R_r = P' - P_r$	P_s	$R_s = P' - P_s$
.01	4	−1	−1	1	−0.8	4.8	0	4	$-\frac{8}{7} = -1.14$	$\frac{36}{7} = 5.14$
.02	8	2	0	1	8.0	0	4	4	$\frac{44}{7} = 6.29$	$\frac{12}{7} = 1.71$
.03	2	1	1	−2	−2.8	4.8	−2	4	$-\frac{10}{7} = -1.43$	$\frac{24}{7} = 3.43$
.04	−2	−1	−1	2	2.8	−4.8	2	−4	$\frac{10}{7} = 1.43$	$-\frac{24}{7} = -3.43$
.05	−8	0	−2	−1	−8.0	0	−4	−4	$-\frac{44}{7} = -6.29$	$-\frac{12}{7} = -1.71$
.06	−4	1	1	−1	0.8	−4.8	0	−4	$\frac{8}{7} = 1.14$	$-\frac{36}{7} = -5.14$
Range	16	3	3	4	16	9.6	8	8	$\frac{88}{7} = 12.57$	$\frac{72}{7} = 10.29$
Sum of squares	168	8	8	12	144.96	92.16	40	96	$\frac{600}{7} = 85.71$	$\frac{576}{7} = 82.29$
Root mean square	5.3	1.2	1.2	1.4	4.9	3.9	2.6	4.0	3.8	3.7

C_r			60%		50%	
$\frac{100R}{\frac{1}{2}(P' + P)}$			60%		66.7%	72.0%
$50R(1/P' + 1/P)$			60%		75%	73.1%
C_s			74.1%		75.6%	70.0%
Q		8.000		4.00		$\frac{44}{7} = 6.286$
q_1		0.275		0.25		$\frac{13}{44} = 0.295$
q_2		0.275		0.25		$\frac{13}{44} = 0.295$
q_3		0.450		0.50		$\frac{9}{22} = 0.409$

the cancellation pattern to the range of the actual lead yields the preferable coefficient for expressing the numerical result of a minimum range cancellation. This same ratio has been used by McFee and Parungao.[11]

Attention may now be directed to the minimum root mean square cancellation, $R_s = P' - P_s$. It is apparent from inspection of this column that the range of this cancellation is 72/7 or 10.29 units, which is larger than the range of 8 units for lead R_r and the range of 9.6 units for lead R_o. However, the root mean square of lead R_s is only 3.70 units and is smaller than the root mean squares of 4.00 units and 3.92 units of lead R_r and lead R_o, respectively. The coefficient, C_s, is 70 per cent and is the smallest value which is obtainable with any combination of leads L_1, L_2, and L_3 used to cancel P′, since P does not appear in the denominator of the ratio determining C_s.

Table II illustrates cancellation patterns which demonstrate several interesting features. The column, P′, contains, at 5 instants of time, arbitrarily selected potentials of a lead to be cancelled by a synthetic lead formed by the three leads, L_1, L_2, and L_3, the arbitrary potentials of which are listed in their respective columns. In this instance it is possible to form three different synthetic leads, P_{r1}, P_{r2}, and P_{r3}, which, when subtracted from P′, produce three different cancellation patterns, R_{r1}, R_{r2}, and R_{r3}, possessing identical minimum ranges. The upper range limit of all three is 2.5 units, and the lower range limit is formed by the zero end points, since all of the cancellation potentials are positive and there are no crossing points. The upper range limits of R_{r1} and R_{r2} are each formed by $(n + 1)$ or four equal potential points, which is the predicted number for a cancellation graph which does not touch the zero base line except at its ends. The upper range limit of R_{r3}, however, is formed by only three equal potential points. This pattern was obtained by setting $|S| = R_{.01} - R_{.02} = R_{.03} - R_{.02} = R_{.03} - R_{.04} = R_{.05} - R_{.04}$. The value of $|S|$ so calculated is 0.75 units, which is less than the 2.5 units representing the actual range of the cancellation graph. The cancellation, R_{r3}, was, therefore, initially rejected as not meeting the criterion for a minimum range pattern. However, when the range of R_{r3} was later compared with those of R_{r1} and R_{r2}, each of which meets the criterion for a minimum range pattern, in that the calculated $|S|$ of each is equivalent to its actual range, it became obvious that all three cancellations possessed the same minimum range. Such a rare example as this prompted the inclusion of Step 6 in the description of the systematic method of computing a minimum range cancellation. This example illustrates the fact that the investigator may theoretically have more than one minimum range cancellation from which to choose. In such a circumstance he might select as preferable that pattern which has the fewest number of potential points located at the range limit. (Thus, in Table II, the preferred minimum range cancellation might be R_{r3}.)

Table II also lists the root mean square cancellation, R_s, formed by subtracting the synthetic lead, P_s, from the actual lead P′. Although the coefficient, C_r, is larger for R_s than the identical values of C_r for the three minimum range cancellations, the latter possess larger values of C_s than is obtained with the root mean square cancellation. The cancellation, R_{r3}, has a C_s which is closer to that

TABLE II (SEE TEXT)

TIME (t) IN SECONDS	POTENTIALS IN ARBITRARY UNITS												
	P′	L_1	L_2	L_3	P_{r1}	$R_{r1} = P' - P_{r1}$	P_{r2}	$R_{r2} = P' - P_{r2}$	P_{r3}	$R_{r3} = P' - P_{r3}$	P_s	$R_s = P' - P_s$
.01	20	−5	5	10	17.5	2.5	17.5	2.5	17.5	2.5	17.38	2.62
.02	30	10	0	6	29.0	1.0	27.5	2.5	28.25	1.75	28.45	1.55
.03	0	5	−5	0	−2.5	2.5	−2.5	2.5	−2.5	2.5	− 2.30	2.30
.04	−30	0	−10	−5	−32.5	2.5	−31.0	1.0	−31.75	1.75	−31.55	1.55
.05	−10	−5	5	−10	−12.5	2.5	−12.5	2.5	−12.5	2.5	−12.78	2.78
Range	60	15	15	20	61.5	2.5	58.5	2.5	60	2.5	60	2.78
Sum of squares	2300	175	175	261	2366	26	2186	26	2274.88	24.88	2275.35	24.67
Root mean square	21.4	5.9	5.9	7.2	21.8	2.3	20.9	2.3	21.3	2.2	21.3	2.2
C_r						4.17%		4.17%		4.17%		4.63%
C_s						10.63%		10.63%		10.40%		10.36%
Q					6.0000		5.7000		5.8500		5.8492	
q_1					0.3333		0.3246		0.3291		0.3318	
q_2					0.4167		0.4123		0.4145		0.4104	
q_3					0.2500		0.2631		0.2564		0.2578	

of R_s than is the C_s of either R_{r1} or R_{r2}, since the pattern of R_s resembles that of R_{r3} more closely than the patterns of either R_{r1} or R_{r2}.

It is of interest that $Q_3 = Qq_3 = 1.5$ for all three minimum range cancellations listed in Table II. The differences between the three patterns is dependent upon differences between the three coefficients, $Q_1 = Qq_1$, and between the three coefficients, $Q_2 = Qq_2$.

The data selected for Tables I and II are admittedly highly artificial and could not be duplicated by cancellations obtained from the living heart or calculated from mathematical models which reasonably represent equivalent heart generators.[9,10] They serve the purpose, however, to demonstrate some interesting, purely mathematical aspects of the cancellation phenomenon.

SUMMARY

1. The concept of electrocardiographic cancellation can be generalized by imposing no limitation on the number of leads utilized in the formation of a synthetic lead for the purpose of cancelling an actual lead.

2. Mathematical methods are given in detail for the computation of two types of cancellation patterns: (a) the minimum root mean square cancellation in which the sum of the squares of the deviations of the potentials from zero is minimized; (b) the minimum range cancellation in which the maximum peak-to-nadir spread of the potential points is minimized.

3. If a synthetic lead is formed by n leads, a cancellation pattern having zero potential at n separate instants of time can always be produced. Therefore the maximum peak and maximum nadir of an actual lead can always be brought to the zero base line by a synthetic lead formed by two or more leads. However, the production of complete cancellation of the upper and lower limiting potentials of an actual lead does not constitute the technique for obtaining either a minimum range or a minimum root mean square type of pattern.

4. Although cancellation patterns usually show multiple zero crossing points, it is mathematically possible for all of the potential points of both a minimum root mean square cancellation and a minimum range cancellation to be grouped on either the positive side or the negative side of the zero base line. Likewise, either type of cancellation pattern may possess only one zero crossing point.

5. The upper and lower limits of a calculated minimum range cancellation are formed by a group of maximally positive and maximally negative potential points, the total number of which exceeds by two the number of leads which form the synthetic lead. If the number of such leads is represented by n, the number of equal and maximally positive potential points may vary from 1 to $(n + 1)$. If the number of these limiting positive potential points is represented by m, the number of equal and maximally negative potential points is $(n + 2)$-m. If a minimum range cancellation consists entirely of either positive or negative points, $(n + 1)$ of the points are both equal and maximally positive or maximally negative. The respective lower or upper limit of the cancellation pattern is then formed by the two zero end points.

6. Suitable means of expressing quantitatively in per cent the results of both minimum root mean square and minimum range cancellations are presented and discussed. It is pointed out that the denominators of such expressions should contain terms referable only to the actual lead rather than to both the actual and synthetic leads.

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Influence of Variations in Dietary Intake of Chlorides Upon Diverse Necrotizing Cardiopathies

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Earlier investigations showed that $MgCl_2$ and KCl are especially active in preventing the Electroyte-Steroid-Cardiopathy characterized by Necroses (*ESCN*). Indeed, these salts prevent the occurrence of not only the typical ESCN (induced by corticoids and certain sodium salts), but also various other experimental lesions of the heart, such as the suppurative myocarditis that is normally elicited by combined treatment with dihydrotachysterol (DHT) + NaH_2PO_4, the necrotizing myocarditis that develops in the corticoid-conditioned animals during exposure to various stressors, and even those cardiac necroses that follow (presumably as a result of direct proteolytic action) intravenous treatment with proteases.[1-4]

Additional experiments indicated that the chlorides of other cations (like NaCl, NH_4Cl, or $CaCl_2$), as well as a mixture of these electrolytes containing equivalent amounts of the anion, are to a certain extent all effective inhibitors of the ESCN and of the infarctoid cardiac changes normally elicited with $NaClO_4$ after sensitization by diets deficient in K or Mg.[5-6] From these facts, we concluded that both the cations (K^+ and Mg^{++}) and the anion (Cl^-) play an important role in the yet unclarified biochemical processes that desensitize the myocardium against diverse potentially cardiotoxic agents. It has also been observed that transient occlusion of the pylorus (accompanied by hypochloremia) regularly elicits acute, massive myocardial necroses in rats suitably conditioned by combined subthreshold doses of methylchlorocortisol + NaH_2PO_4.[7]

In the work to be reported here, we examined the participation of the Cl-ion in the pathogenesis of necrotizing cardiopathies by varying the dietary intake of chlorides. Rats kept on a high- or low-chloride diet were subsequently treated with diverse cardiotoxic agents. The pathogenic agents used were: (1) noradrenalin and vasopressin (agents capable of producing "spotty myolysis,"

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with disappearance of muscle-fiber segments but without extensive necroses or inflammation); (2) plasmocid (a rather toxic, and now obsolete, antimalarial that produces large, patchy, myocardial necroses and myocarditic lesions); (3) papain (because this proteolytic enzyme preparation elicits acute, miliary, disseminated myocardial necroses); (4) DHT, a steroid of the vitamin D group (because it causes intense calcium deposition in the heart and in the coronary arteries); (5) DHT + Ca-acetate (since this combined treatment results in acute, suppurative myocarditis); (6) fluorocortisol + Na_2HPO_4 (since this combination is highly effective in producing a typical ESCN characterized by massive, infarct-like cardiac necroses, with secondary inflammation but without any demonstrable histologic change in the structure of the coronary arteries); (7) fluorocortisol + Na-acetate (a treatment very effective in sensitizing the myocardium to the necrotizing actions of stress, but which, in itself, never elicits histologically demonstrable cardiac damage); (8) nonspecific stressor agents such as forced restraint or quadriplegia (which are capable of producing necrotic foci, especially in the corticoid-conditioned animals). The histologic characteristics of the experimental cardiopathies elicited by these agents more or less closely imitate certain spontaneous myocardial changes in man; they have been described in detail elsewhere.[1-3,8,9]

MATERIALS AND METHODS

Experiments With a Low-Chloride Diet.—Two hundred and twenty female Sprague-Dawley rats, with an average initial body weight of 50 grams (range: 45 to 56 grams), were subdivided into 22 equal groups and treated as indicated in Table I.

The experimental animals (even-numbered groups) were kept on a low-chloride diet, whereas the controls (odd-numbered groups) received a basic diet, throughout the period of observation.* In this manner, we hoped to eliminate any possible nonspecific effect that might have been due to the pure synthetic diet. The rats on the low-chloride diet received distilled water ad libitum to drink; those on the basic diet received tap water.

The *composition of the basic diet* was as follows:

Sucrose	70.65%
Vitamin-free test casein GBI	18.30%
Butter fat (salt free)	5.00%
Vitamin supplement (see below)	1.05%
Salt mixture (see below)	5.00%
Vitamin supplement (grams/100 lb. of diet)	
Alpha tocopherol	10.215
Calcium pantothenate	2.043
Carotene in oil, 3,333 U./gram	150.000
Choline dihydrogen citrate	272.400
i-Inositol	13.620
Menadione	0.102
Niacin	27.240
Pyridoxine phosphate	0.953
Riboflavin	0.953
Thiamine monophosphate	0.953
Viosterol 400,000 U./gram	0.125

*The diets used in these experiments were supplied by General Biochemicals, Inc., Chagrin Falls, Ohio.

Salt mixture

Calcium lactate	20.400%
Calcium gluconate	12.000%
Potassium phosphate (monobasic)	11.200%
Potassium chloride	31.200%
Sodium phosphate (dibasic)	2.500%
Sodium chloride	4.974%
Sodium bicarbonate	2.500%
Ferric citrate	9.500%
Magnesium chloride	3.800%
Copper sulfate	1.900%
Zinc acetate	0.026%

The *composition of the low-chloride diet* differed from the basic diet only as regards the salt mixture:

Calcium lactate	20.400%
Calcium gluconate	12.000%
Potassium phosphate (monobasic)	11.200%
Potassium bicarbonate	31.200%
Sodium phosphate (dibasic)	2.500%
Sodium bicarbonate	7.474%
Ferric citrate	9.500%
Magnesium oxide	3.800%
Copper sulfate	1.900%
Zinc acetate	0.026%

The total chloride content of the low-chloride diet was 0.035 per cent, whereas that of the basic diet was 0.935 per cent (according to the data given by General Biochemicals, Inc.). Reports in the literature show that diets deficient in chlorides retard somatic growth, in the rat.[10] We therefore carried out preliminary studies designed to confirm this finding, using our low-chloride diet. It was seen that the growth rate of rats on this diet was diminished as compared with that of control rats on the basic diet; this difference was, however, significant only after the twentieth day.

Preliminary experiments, on animals of similar body weight, showed that the doses of the various cardiotoxic agents used here produce only slight cardiac damage, if any. Hence, these doses were suitable for demonstrating possible sensitization by the low-chloride diet. The potentially cardiotoxic agents used were the following: noradrenalin, vasopressin, plasmocid, papain, dihydrotachysterol, calcium acetate, fluorocortisol, Na_2HPO_4, sodium acetate, restraint, and quadriplegia.

Noradrenalin was given at the dose of 150 μg in 0.2 ml. of oil, twice daily, subcutaneously, on the seventeenth and eighteenth days of the experiment. *Vasopressin** was injected twice daily on the seventeenth and the following day, at the dose of 10 I.U. in 1.0 ml. of water, subcutaneously. *Plasmocid*, 6-methoxy-8-(3-diethyl-amino-propylamino)-quinoline dihydroiodide, was injected three times daily, at 4-hour intervals, on the seventeenth and eighteenth days, at the dose of 0.3 mg. in 0.2 ml. of water, intraperitoneally. *Papain:* Five grams of crude papain powder† were added to 50 ml. of distilled water; this turbid suspension was mixed in a Waring Blendor for 10 minutes and then passed through a No. 40 Whatman filter paper. Of the resulting clear, amber-colored filtrate, 0.1 ml. was injected into the jugular vein, under light ether anesthesia, once on the seventeenth day. *Dihydrotachysterol*, or DHT, was always given in the form of a microcrystal suspension, twice daily, by stomach tube. This treatment was administered from the thirteenth to the eighteenth day of the experiment. The rats in Groups XI and XII received 70 μg of DHT daily, in two equal portions, always in 1.0 ml. of water. In Groups XIII and XIV, 20 μg of DHT

*Parke, Davis & Company.
†Fisher Scientific Company.

were administered mixed with Ca-acetate, in 1.0 ml. of water, twice daily. *Calcium acetate** was given (together with DHT) in a concentration of 0.25 mM. in 1.0 ml. of water, twice daily, by stomach tube, between the thirteenth and eighteenth days. *Fluorocortisol*, 9α-fluorohydrocortisone acetate, was injected subcutaneously, as a microcrystal suspension, at the dose of 500 μg daily, in 0.2 ml. of water, from the thirteenth to the eighteenth days. Na_2HPO_4, dibasic sodium phosphate* was administered from the thirteenth to the eighteenth days, in a concentration of 0.25 mM. in 1.0 ml. of water, twice daily, by stomach tube. *Sodium acetate** was likewise given by stomach tube, twice daily, in a concentration of 0.25 mM. in 1.0 ml. of water from the thirteenth to the eighteenth day. *Restraint* was applied on the seventeenth day by strapping the rats with adhesive tape to a board, in the prone position, for 17 hours. *Quadriplegia*, through motor denervation of all four extremities, was performed on the seventeenth day, under ether anesthesia. Both cervical plexuses, as well as the femoral, obturator, and sciatic nerves were severed.

The experiment was terminated on the nineteenth day by killing the surviving rats with chloroform. In all instances, the hearts were first inspected with the aid of a dissecting loupe, immediately after autopsy, and then fixed in absolute alcohol, containing 10 per cent neutral formalin, for subsequent embedding in paraffin. The sections were stained with von Kóssa's technique for the histochemical demonstration of calcium (using hematoxylin-phloxine counterstain), as well as with our fuchsin method,[1] which shows prenecrotic changes in the myocardium. The severity of the lesions was assessed in an arbitrary scale of 0 to 3, depending upon the intensity of the cardiac lesions (necrosis, inflammation, calcification). In Table I, we list the means of these determinations (with standard errors), as well as the percentual mortality rate of each group.

Experiments With a High-Chloride Diet.—To observe the effect of a high-chloride diet upon the development of necrotizing cardiopathies, 200 female Sprague-Dawley rats, with a mean initial body weight of 51 grams (range: 46 to 58 grams), were subdivided into 20 equal groups and treated as indicated in Table II.

All the animals of the odd-numbered groups (listed in Table II) were maintained on a synthetic basic diet, whereas those of the even-numbered groups were kept on a high-chloride diet. The total chloride content of the high-chloride diet was 1.62 per cent (as determined by General Biochemicals, Inc.). The *basic diet* used here was identical in its composition with that described for the first experimental series. The composition of the *high-chloride diet* differed from the basic diet only as regards the salt mixture, which consisted of:

Calcium chloride	32.400%
Potassium phosphate (monobasic)	11.000%
Potassium chloride	31.200%
Sodium phosphate (dibasic)	2.500%
Sodium chloride	7.474%
Ferric chloride	9.500%
Magnesium chloride	3.800%
Copper chloride	1.900%
Zinc chloride	0.026%

In order to establish the possible protective effect of the high-chloride diet, the doses of the cardiotoxic agents (with the exception of noradrenalin, vasopressin, and fluorocortisol) were higher than in the previous experimental series: namely, plasmocid, 0.5 mg.; papain, 0.15 ml. (10 per cent); DHT, 100 μg to Groups XI and XII, and 75 μg to Groups XIII and XIV; Ca-acetate, 0.5 mM.; Na-acetate, 1 mM.; and Na_2HPO_4, 0.5 mM. However, the date of initiation, duration of treatment, route of administration, and all other experimental conditions remained the same as previously.

Because of the high mortality rate, the surviving rats of Groups XIII and XIV were killed on the seventeenth day; all animals in the other groups were sacrificed on the nineteenth day, the termination of the experiment. The results were evaluated histologically, as previously described, and are summarized in Table II.

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*Fisher Scientific Company.

RESULTS

Effect of Low-Chloride Diet (Figs. 1-3).—As will be seen from the data in Table I, chloride-deficiency markedly enhanced the cardiotoxic effect of most of the agents used. Only the necrotizing actions of noradrenalin and vasopressin were not affected.

TABLE I. EFFECT OF LOW-CHLORIDE DIET UPON CARDIAC LESIONS PRODUCED BY SMALL DOSES OF VARIOUS AGENTS

GROUP	TREATMENT	CARDIAC LESIONS		MORTALITY (%)
		GRADE (0-3)	INCIDENCE (%)	
I	Basic diet	0	0	0
II	Low-chloride diet	0	0	0
III	Noradrenalin + basic diet	1.1 ± 0.27	60	0
IV	Noradrenalin + low-chloride diet	1.0 ± 0.20	60	0
V	Vasopressin + basic diet	1.3 ± 0.31	60	0
VI	Vasopressin + low-chloride diet	1.5 ± 0.23	70	0
VII	Plasmocid + basic diet	0.3 ± 0.18	20	0
VIII	Plasmocid + low-chloride diet	2.7 ± 0.13	90	40
IX	Papain + basic diet	0.4 ± 0.17	30	0
X	Papain + low-chloride diet	2.8 ± 0.20	100	50
XI	Dihydrotachysterol + basic diet	0.2 ± 0.20	20	0
XII	Dihydrotachysterol + low-chloride diet	3.0 ± 0	100	60
XIII	Dihydrotachysterol + Ca-acetate + basic diet	0.5 ± 0.25	30	0
XIV	Dihydrotachysterol + Ca-acetate + low-chloride diet	3.0 ± 0	100	40
XV	Fluorocortisol + Na_2HPO_4 + basic diet	0.3 ± 0.18	20	0
XVI	Fluorocortisol + Na_2HPO_4 + low-chloride diet	2.7 ± 0.21	100	100
XVII	Fluorocortisol + Na-acetate + basic diet	0	0	0
XVIII	Fluorocortisol + Na-acetate + low-chloride diet	2.2 ± 0.13	90	70
XIX	Fluorocortisol + restraint + basic diet	0.8 ± 0.25	50	0
XX	Fluorocortisol + restraint + low-chloride diet	2.6 ± 0.15	100	20
XXI	Fluorocortisol + quadriplegia + basic diet	0.2 ± 0.20	10	0
XXII	Fluorocortisol + quadriplegia + low-chloride diet	1.9 ± 0.26	90	10

The body weights of the animals maintained on the experimental and on the basic diets were essentially the same at the time when treatment with the various cardiotoxic agents began, yet the low-chloride diet markedly aggravated the severity and incidence of the cardiac lesions normally produced by plasmocid (Groups VII and VIII), papain (Groups IX and X), DHT (Groups XI and XII), DHT + Ca-acetate (Groups XIII and XIV), fluorocortisol + Na_2HPO_4 (Groups XV and XVI), fluorocortisol + Na-acetate (Groups XVII and XVIII), as well as those elicited by restraint (Groups XIX and XX) and quadriplegia (Groups XXI and XXII), after conditioning with fluorocortisol.

The comparatively small doses of *plasmocid*, which produced only occasional, mild lesions in the control rats, regularly caused large, patchy myocardial necroses and myocarditic lesions in the chloride-deficient animals. It will be recalled that the plasmocid lesions differ from most of the other experimental cardiopathies that we studied in that the former cannot be greatly influenced by treatment with electrolytes or corticoids. Nevertheless, as in many other cardiopathies,

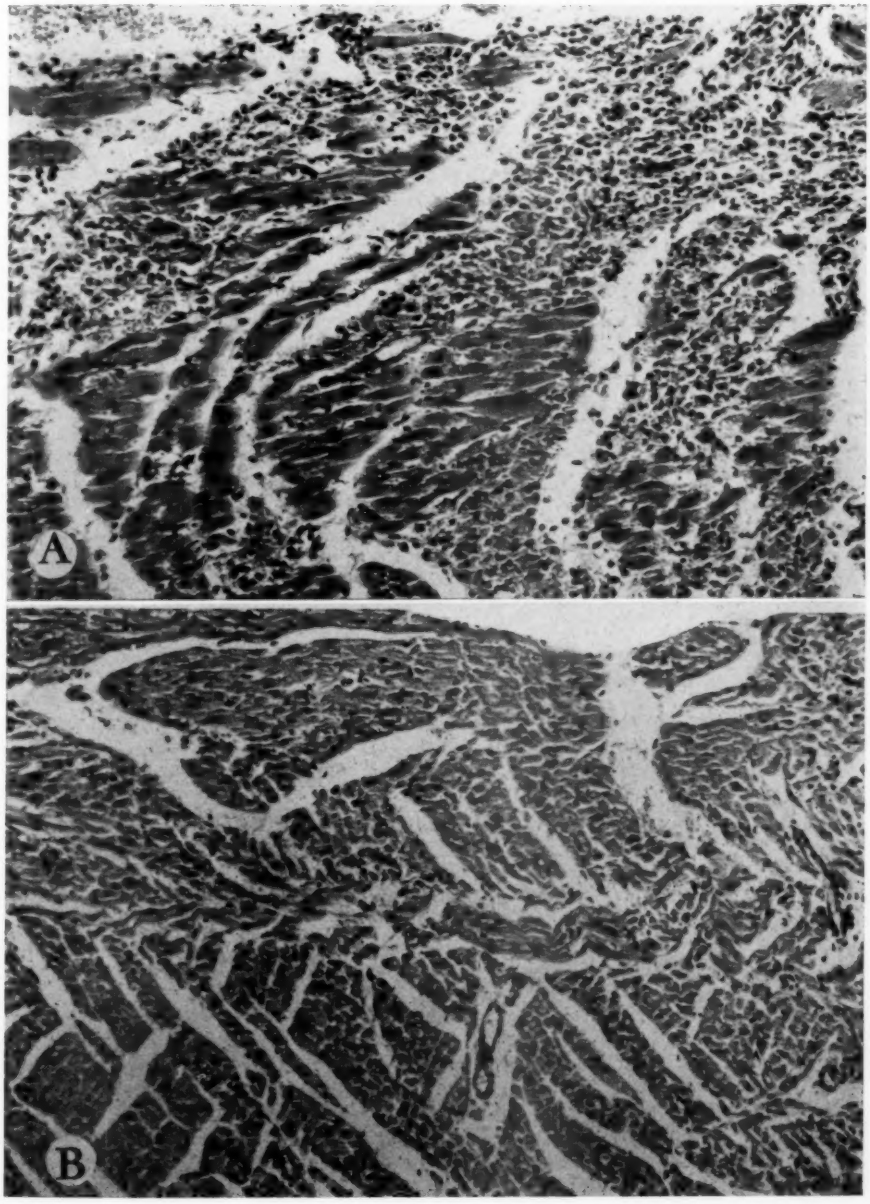

Fig. 1.—Sensitization by low-chloride intake to necrotizing effect of papain. *A*, Extensive necroses throughout the wall of the right ventricle, in a papain-treated rat kept on a chloride-deficient diet. *B*, Absence of cardiac lesions in a similarly papan-tri ated control rat allowed a normal intake of chlorides (von Kóssa, × 120).

Na-deficiency offered protection against plasmocid also.[11] The miliary, disseminated cardiac necroses normally caused by the intravenous injection of *papain* were much more severe in the rats kept on a chloride-deficient diet; this sensitization also manifests itself in the mortality rate (Table I). Chloride-deficiency not only aggravated the calcification and necrosis of the cardiac muscle normally produced by *DHT*, but intensive calcification also occurred in the skeletal muscles, gastrointestinal tract, and renal cortex. The calcification of

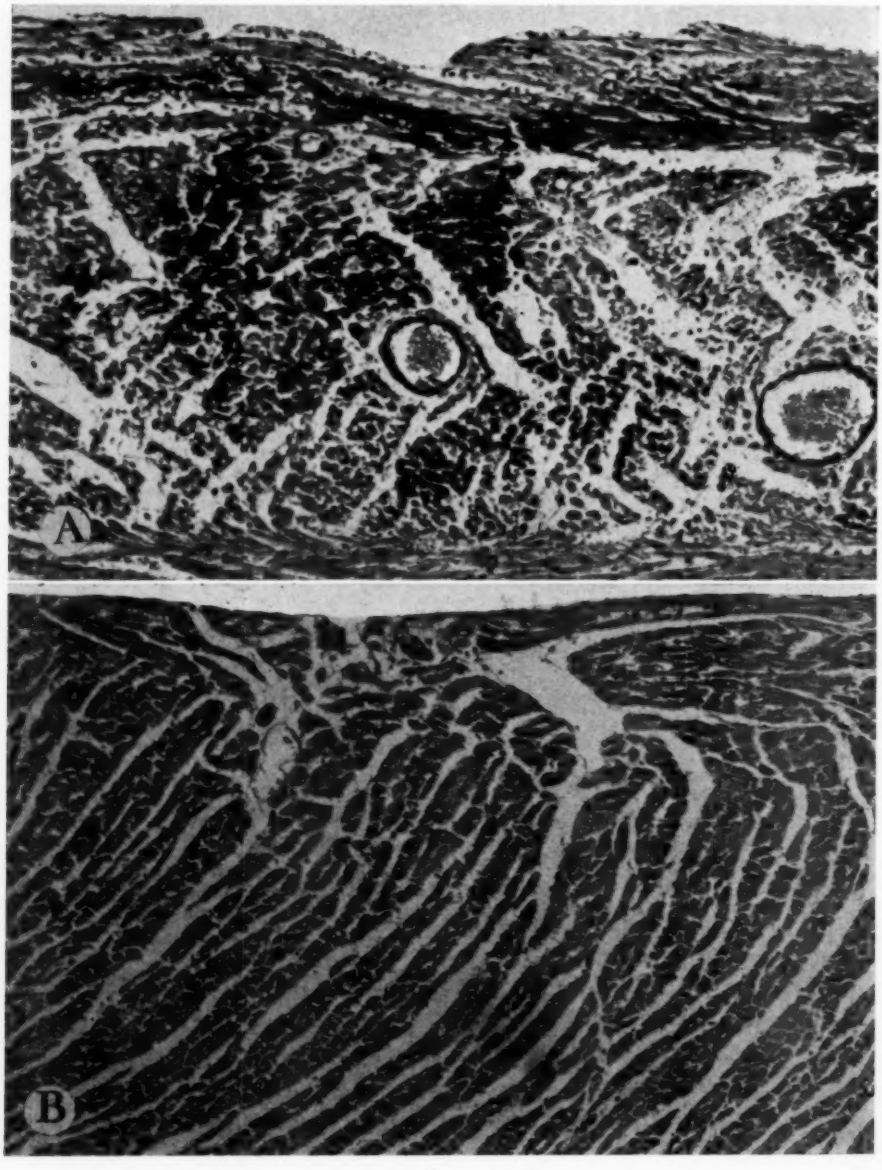

Fig. 2.— Sensitization by low-chloride diet to calcifying action of DHT. *A*, Intensive calcification of the myocardium and coronary vessels of a DHT-treated rat sensitized by a low-chloride diet. *B*, No calcification after similar treatment with DHT in a control rat maintained on a basic diet (von Kóssa, ×120).

the tissues was even more marked in the chloride-deficient rats treated with *DHT + Ca-acetate*; in these animals, muscular paralysis developed in addition to acute, suppurative myocarditis. The combination of Na_2HPO_4 + *fluorocortisol* in the amounts used was not sufficient to induce ESCN in the control rats, whereas 100 per cent of the chloride-deficient animals died, exhibiting the typical picture of this infarctoid cardiopathy. It is especially interesting, furthermore, that in the animals kept on the low-chloride diet, otherwise completely ineffective treatment with *fluorocortisol + Na-acetate* elicited macroscopically visible, large patches of cardiac necroses resembling the typical ESCN. Nephrocalcinosis developed in many, but not in all, of these rats. The *stressor effect* of neuromuscular effort (induced by forced restraint) or quadriplegia only occasionally produced the usual small necrotic foci ("micronecroses") in the control animals conditioned with *fluorocortisol*; but here again, dietary chloride-deficiency sensitized the heart muscle so that, as a result of stress, large, macroscopically visible necroses developed.

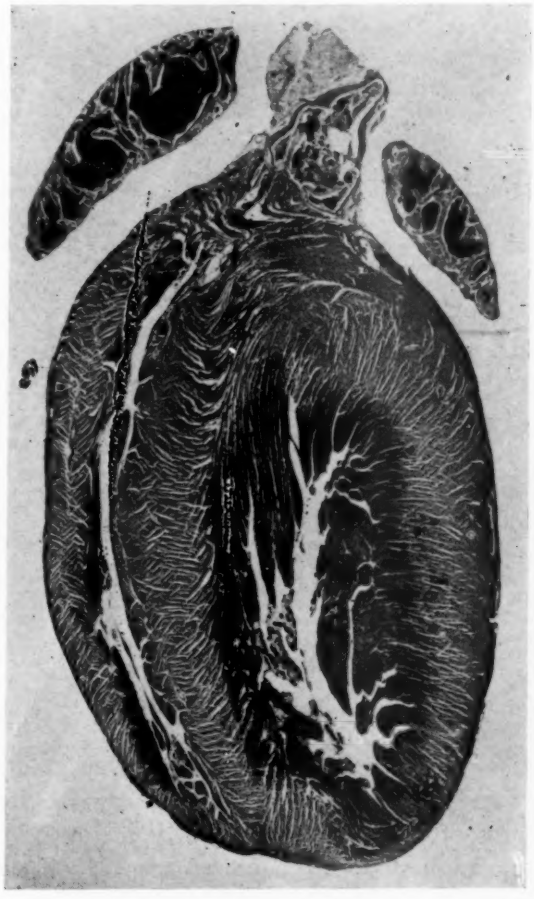

Fig. 3.—Sensitization by chloride-deficiency to the necrotizing action of fluorocortisol + Na-acetate. The general view of the myocardial necrosis and calcification (*black area*) in a rat given fluorocortiso + Na-acetate while on a low-chloride diet. On a normal diet this treatment is consistently ineffective in producing any cardiac lesion without subsequent exposure to stressor agents (von Kössa, ×9).

On the other hand, the spotty, myolytic type of cardiac damage elicited with *noradrenalin* (Groups III and IV) and with *vasopressin* (Groups V and VI) was not altered by a lowered dietary intake of chlorides.

Effect of High-Chloride Diet (*Figs. 4-6*).—As shown in Table II, an increase in the dietary intake of chlorides from a basic 0.953 to 1.62 per cent protects the myocardium against the necrotizing actions of many unrelated agents. Here again, however, the cardiotoxicity of noradrenalin and of vasopressin was not significantly influenced.

TABLE II. EFFECT OF HIGH-CHLORIDE DIET UPON CARDIAC LESIONS PRODUCED BY LARGE DOSES OF VARIOUS AGENTS

GROUP	TREATMENT	CARDIAC LESIONS		MORTALITY (%)
		GRADE (0-3)	INCIDENCE (%)	
I	Basic diet	0	0	0
II	High-chloride diet	0	0	0
III	Noradrenalin + basic diet	0.4 ± 0.28	30	0
IV	Noradrenalin + high-chloride diet	0.5 ± 0.25	40	0
V	Vasopressin + basic diet	0.8 ± 0.37	50	0
VI	Vasopressin + high-chloride diet	1.1 ± 0.21	70	0
VII	Plasmocid + basic diet	2.9 ± 0.12	100	80
VIII	Plasmocid + high-chloride diet	0.4 ± 0.16	20	0
IX	Papain + basic diet	3.0 ± 0	100	90
X	Papain + high-chloride diet	0.5 ± 0.23	30	10
XI	Dihydrotachysterol + basic diet	2.6 ± 0.34	100	20
XII	Dihydrotachysterol + high-chloride diet	0.2 ± 0.20	10	10
XIII	Dihydrotachysterol + Ca-acetate + basic diet	3.0 ± 0	100	70
XIV	Dihydrotachysterol + Ca-acetate + high-chloride diet	0.6 ± 0.27	40	0
XV	Fluorocortisol + Na_2HPO_4 + basic diet	2.1 ± 0.18	90	50
XVI	Fluorocortisol + Na_2HPO_4 + high-chloride diet	0	0	100
XVII	Fluorocortisol + Na-acetate + restraint + basic diet	2.8 ± 0.16	100	70
XVIII	Fluorocortisol + Na-acetate + restraint + high-chloride diet	0.2 ± 0.17	10	70
XIX	Fluorocortisol + restraint + basic diet	1.0 ± 0.39	60	40
XX	Fluorocortisol + restraint + high-chloride diet	0.1 ± 0.10	10	30

The mean body weight of the rats kept on the basic and high-chloride diets was essentially the same at the initiation of the cardiac-damaging treatments. Yet, the dietary excess of chlorides significantly protected the animals against the cardiac lesions normally produced by plasmocid (Groups VII and VIII), papain (Groups IX and X), DHT (Groups XI and XII), and DHT + Ca-acetate (Groups XIII and XIV). Not only the decrease in the severity and incidence of the cardiac lesions, but also the lowered mortality rate, illustrates the desensitizing action of a high intake of chlorides in all four cardiopathies. It is especially

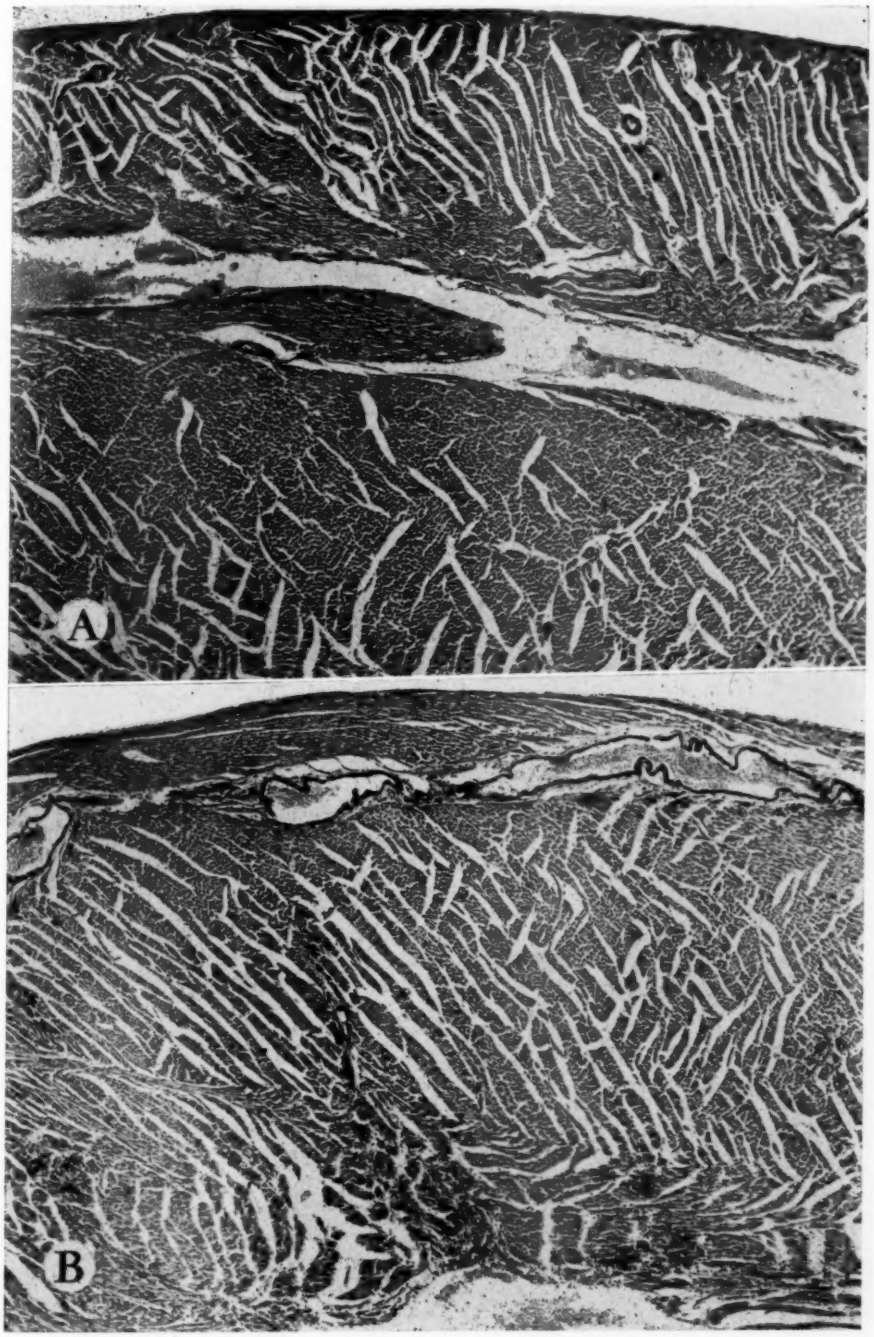

Fig. 4.—Prevention by high-chloride diet of cardiac calcification after DHT treatment. *A*, Absence of calcification and necrosis in heart of a rat kept on high-chloride diet and given a large amount of DHT. *B*, Severe calcifying lesions produced by same doses of DHT on the basic diet (von Kóssa, ×30).

noteworthy that a dietary excess of chlorides abolished the cardiotoxic action of DHT and that of DHT + Ca-acetate; in an earlier experiment, Na-deficiency similarly inhibited the calcifying and slight necrotizing actions of DHT, but not the more severe myocarditic lesions resulting from DHT + Ca-acetate.[11] Interestingly, in the animals treated with DHT, as well as in those treated with DHT + Ca-acetate, the high-chloride diet suppressed the exclusively cortical nephrocalcinosis normally induced by overdosage with this vitamin-D derivative.

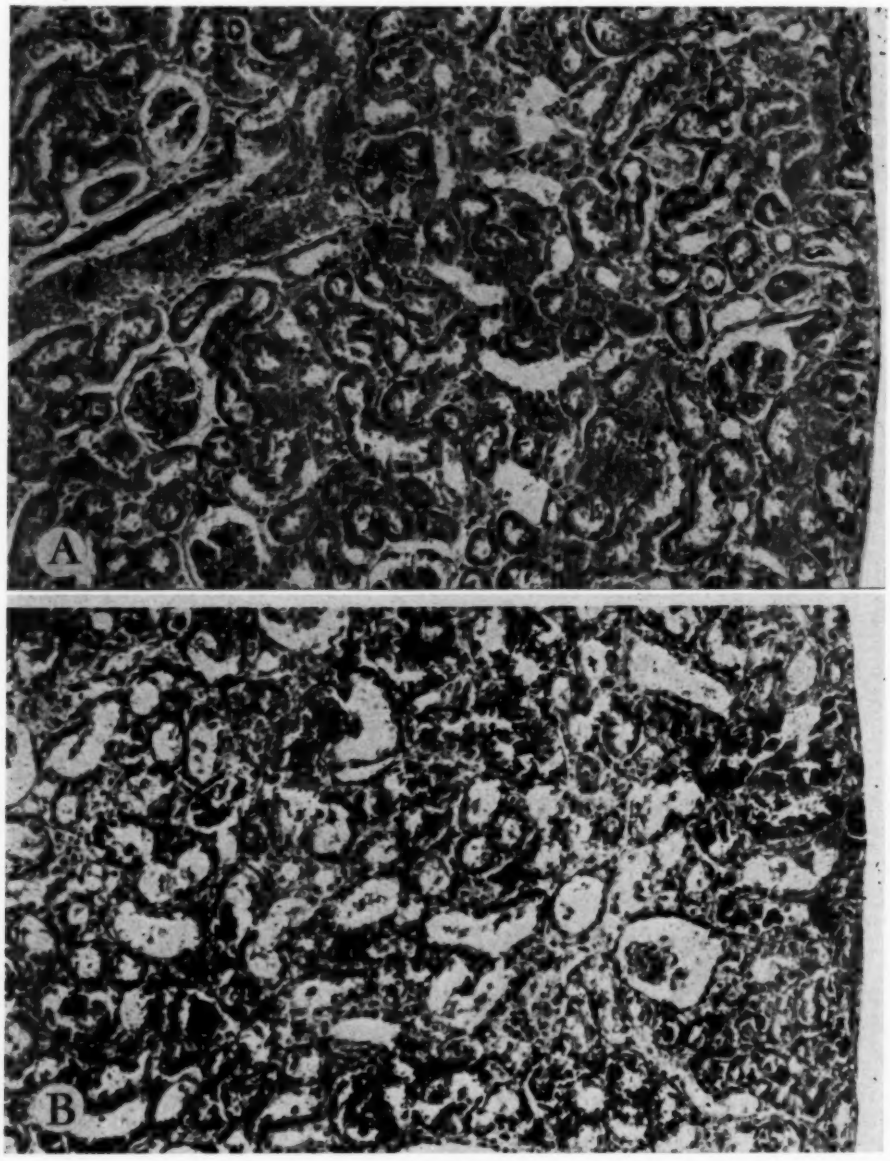

Fig. 5.—Prevention by high-chloride diet of nephrocalcinosis after DHT treatment. *A*, Absence of nephrocalcinosis in rat receiving large doses of DHT while on high-chloride intake. *B*, Marked cortical calcification in the kidney of a similarly DHT-treated animal allowed a normal chloride intake (von Kóssa, ×120).

Many of the animals that were fed the high-chloride diet died after the first injection of fluorocortisol, with rather persistent, tonic extensor cramps. The mortality rate was the highest in the rats receiving a dietary excess of chlorides and treated with fluorocortisol + Na_2HPO_4; here, the clinical picture of acute phosphate intoxication was the dominant feature and resulted in 100 per cent fatality within a few hours. Since these animals did not show any histologically detectable cardiac changes, this part of the experiment is rather inconclusive (Groups XV and XVI). The results obtained in the rats pretreated

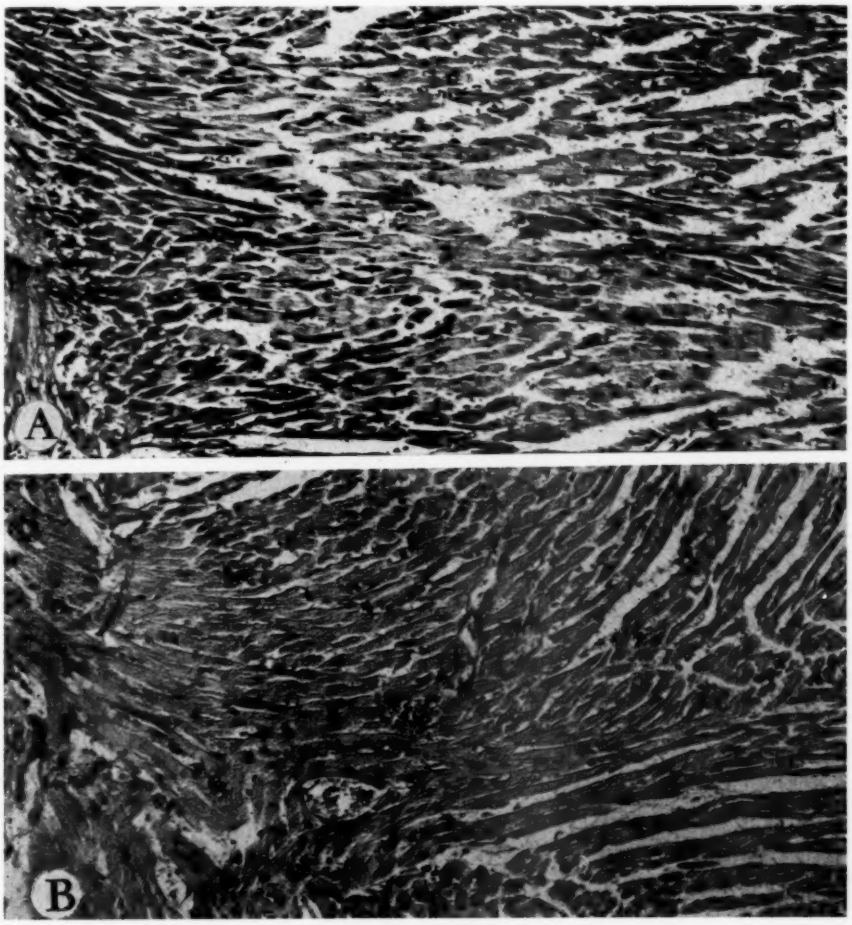

Fig. 6.—Prevention of fuchsinophilic degeneration of myocardium normally caused by stress after sensitization with fluorocortisol + Na-acetate. *A*, Intensive fuchsinophilic degeneration (*dark area*) caused by stress (i.e., restraint) after conditioning with fluorocortisol + Na-acetate. *B*, Inhibition of this change by high-chloride intake (acid fuchsin, ×120).

with fluorocortisol + Na-acetate (Groups XVII and XVIII), and especially in those conditioned with fluorocortisol alone (Groups XIX and XX) and then exposed to the stressor effect of forced restraint, are more instructive, since here the unexpected side actions of fluorocortisol resulted in only 40 and 20 per cent mortality, respectively, among the rats with a high intake of chlorides. None of

the survivors showed marked myocardial damage, whereas in the control animals the lesions were constant and pronounced.

On the other hand, a dietary excess of chlorides did not prevent the occurrence of spotty myolysis in the rats treated with noradrenalin (Groups III and IV) and in those treated with vasopressin (Groups V and VI). The lesions (more or less complete disappearance of individual muscle fibers) induced with these agents were mild in the control animals, but as a result of a high intake of chlorides, their incidence seemed to be slightly increased, although this apparent sensitization was not statistically significant.

DISCUSSION

It is obvious from the observations described in this paper that dietary chloride-deficiency sensitizes the heart to various potentially cardiotoxic agents, whereas dietary chloride-excess exerts an opposite action. Nothing is known as yet about the mechanism through which variations in the dietary intake of chlorides so uniformly influence (aggravate or prevent) the various types of necrotizing cardiopathies that formed the subject of our investigations.

Although the diets used in the present experimental series were identical as regards the ratios and amounts of cations, the variations in their chloride content naturally necessitated changes in other anions. The chloride-deficient diet differed from the basic diet in that in the former the chloride was replaced by equivalent quantities of corresponding bicarbonates. Therefore, since the bicarbonate is generally considered innocuous,[12,13] the noxious effect of this diet may be attributed to its deficiency in chlorides. On the other hand, the great increase in the intake of chlorides with no change in the ratio of cations resulted in a high-chloride diet relatively deficient in bicarbonate and inorganic sulfate. However, the uniform and dramatic preventive effect of this high-chloride diet as compared with the marked opposite effect of chloride-deficiency suggests that the variations in this anion may be the most important factor responsible for the results observed. This assumption is further supported by earlier findings in which, among the various electrolytes administered, no salts of anions other than chlorides offered significant protective action in the ESCN or in other experimental cardiopathies.[1]

All these observations suggest that chlorides play an important role in the pathogenesis of many types of experimental cardiopathies produced by biochemical means. It remains to be established whether variations in the intake of chlorides similarly influence the occurrence of spontaneous necrotizing cardiopathies in man, especially those unaccompanied by acute obstruction of the coronary vessels.

The pathogenesis of the necrotizing cardiopathy normally produced with noradrenalin and vasopressin (changes to which we usually refer as "spotty myolysis") seems to be basically different from all other types of cardiac necroses studied, since only the latter were significantly influenced by the administration of electrolytes, by dietary Na-deficiency,[6,11] or by variations in dietary intake of chlorides. It is interesting in this connection that Raab[14] concluded from his

experiments that a sudden liberation of catecholamines within the heart muscle fibers could be responsible for the development of the ESCN. By depleting the catecholamines with reserpine, he succeeded in protecting the myocardium against this type of necrosis. Perhaps noradrenalin and vasopressin act at the final stage of the biochemical chain-reaction that results in necroses, whereas all other agents (steroids and electrolytes) exert their influence at intermediate points. Yet it would be difficult to explain on this basis why pretreatment with KCl and $MgCl_2$ offers considerable protection against the myocardial necroses normally produced by intravenous administration of proteases[3,4,15] and even against the acute infarcts that follow surgical occlusion of coronary vessels.[16]

SUMMARY

Experiments on rats were performed to examine the effect of variations in dietary intake of chlorides upon diverse experimental cardiac lesions, which differ widely from each other in both their causative agents and their histologic characteristics.

It was found that chloride-deficiency significantly enhances the susceptibility of the heart to the production of necrosis, inflammation, and/or calcification by plasmocid, papain, dihydrotachysterol, Ca-acetate + dihydrotachysterol, Na_2HPO_4 + fluorocortisol, Na-acetate + fluorocortisol, as well as by the stressor effect of forced restraint or quadriplegia after conditioning with fluorocortisol. On the other hand, a dietary excess of chlorides proved to be effective in protecting the myocardium against all the cardiotoxic agents enumerated above.

The observation that a number of diverse cardiopathies are uniformly aggravated by a low-chloride diet, and prevented by a dietary excess of chlorides, suggests that chlorides may play an important role in the pathogenesis of various necrotizing cardiopathies.

The spotty myolysis normally due to the administration of noradrenalin or vasopressin remained uninfluenced by variations in the dietary intake of chlorides; hence, it was concluded that this type of cardiac lesion differs basically in its mechanism from all the other forms studied.

The technical assistance of Miss Therese Demjen is gratefully acknowledged. The authors are also grateful to Dr. R. C. Elderfield, University of Michigan, Ann Arbor, for the generous supplies of plasmocid; to the Sterling-Winthrop Research Institute, for noradrenalin; to the Dr. A. Wander, A. G., for dihydrotachysterol "Calcamin"; to the Upjohn Company, Kalamazoo, Mich., for 9α-fluorocortisol.

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Case Reports

Congenital Vascular Ring: Report of a Case With Survival to 62 Years

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This case of a congenital vascular ring is presented because of its bearing on the natural course of the disease. The patient had symptoms associated with a congenital malformation of the aortic-arch system since early childhood, yet she lived for 62 years.

REPORT OF CASE

The patient was a woman who was 54 years old when she first was examined by one of us (H.M.R.) in November, 1951. In a previous routine roentgenographic survey, a shadow in the superior mediastinum had been interpreted as an aneurysm of the ascending aorta. Since early childhood, the patient had experienced coughing spells, choking sensations, and shortness of breath. She had undergone five illnesses that had been diagnosed as pneumonia, with bronchial asthma also being considered. Periodic episodes of vomiting had occurred early in her life; later, dysphagia had been a more or less constant complaint. In childhood, the patient had lived in constant fear of choking spells, and frequently would awaken at night with the sensation of being strangled. No benefit had been obtained from medicaments prescribed for choking, vomiting, or "asthma." The patient's mother had been found to have a congenitally short esophagus with a large hiatal hernia.

Results of physical examination were not unusual. The blood pressure was 130 mm. Hg systolic and 80 mm. Hg diastolic in both arms. The thyroid was not enlarged. Murmurs were absent, and the lungs were clear on auscultation. The abdomen was normal. Minimal ankle edema was present.

Roentgenoscopic examination revealed the presence of a right aortic arch. There was no demonstrable cardiac enlargement. Roentgenograms of the thorax also disclosed a right aortic arch (Fig. 1). Administration of barium showed severe constriction of the posterior aspect of the esophagus by the retroesophageal aorta (Fig. 2).

Erythrocytes numbered 4,200,000 per cubic millimeter of blood, and the hemoglobin measured 11.5 Gm. per 100 ml. The differential cell count was normal. Electrocardiograms revealed evidence of disease consistent with chronic cor pulmonale.

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During the subsequent 2 years, increasing dyspnea and congestive cardiac failure developed. The choking spells continued. Despite administration of digitalis, ammonium chloride, and meralluride (Mercuhydrin) sodium, the patient's condition became worse. She was hospitalized in 1953 for re-evaluation, and the question of surgical relief of the vascular ring was discussed. In view of her general condition, she declined surgical intervention.

Until her death in May, 1959, the patient was under supervision for dyspnea, choking, and intractable edema of the lower extremities. Meperidine (Demerol) hydrochloride was the only agent that gave symptomatic relief of the choking and shortness of breath. She became addicted to this drug before her death.

Pathologic Features.—At necropsy, the pertinent findings were confined to the heart and great vessels. The heart displayed moderate coronary atherosclerosis. The aortic-arch system was anomalous.

The ascending aorta was continuous with an aortic arch that curved over the right main bronchus and, after reaching the posterior mediastinum, deviated behind the esophagus to the left of the midline, where it became continuous with a somewhat tortuous descending aorta. The descending aorta lay principally to the left side and slightly behind the esophagus (Fig. 3).

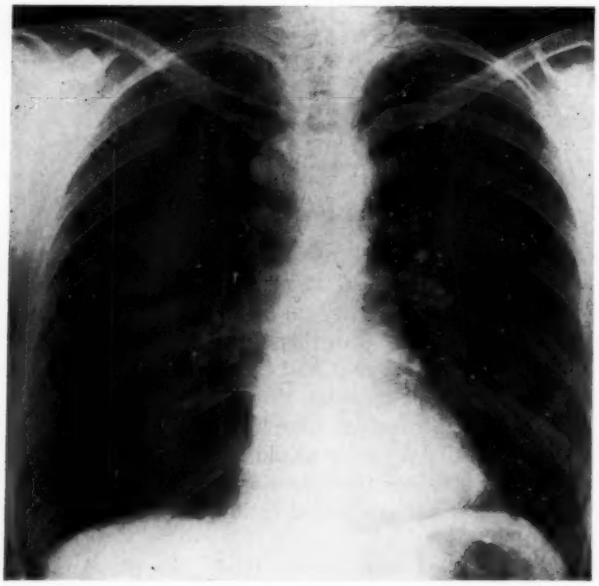

Fig. 1.—Roentgenogram showing the right aortic arch, with a retroesophageal segment and a tortuous descending aorta.

At the left upper angle of the junction between the right arch and the descending aorta was a diverticulum that presented anteriorly (Fig. 4). From the upper end of this diverticulum arose the left subclavian artery. The upper insertion of the ligamentum arteriosum was located at the lower end of the diverticulum, opposite the origin of the left subclavian artery. The lower insertion of the ligamentum was into the left pulmonary artery. The branches of the aortic arch were in the following order from before backward: the left common carotid artery, the right common carotid artery, the right subclavian artery, and the left subclavian artery.

These vascular structures created a "vascular ring" around the trachea and the esophagus; the greatest effect was on the esophagus, which showed pronounced compression from behind forward at the level of the retroesophageal segment of the right aortic arch.

Fig. 2.—Lateral roentgenogram of thorax and esophagus. The large filling defect in the esophagus in the upper part of the thorax is caused by the retroesophageal segment of the right aortic arch.

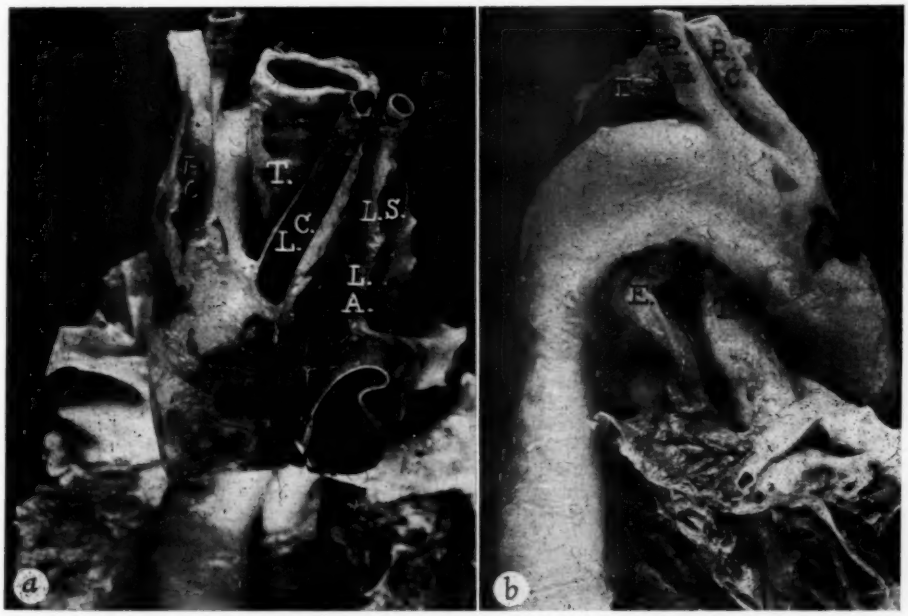

Fig. 3.—*a*, Anterior view of great vessels and mediastinal structures. The ascending aorta joins the aortic arch, which passes over the right bronchus. *T.:* Trachea. *R.C.:* Right common carotid artery. *R.S.:* Right subclavian artery. *L.S.:* Left subclavian artery. *L.C.:* Left common carotid artery. *L.A.:* Ligamentum arteriosum. *b*, Mediastinal structures and great vessels viewed from the right. The aortic arch passes over the right main bronchus and in close relationship to the esophagus (*E.*)

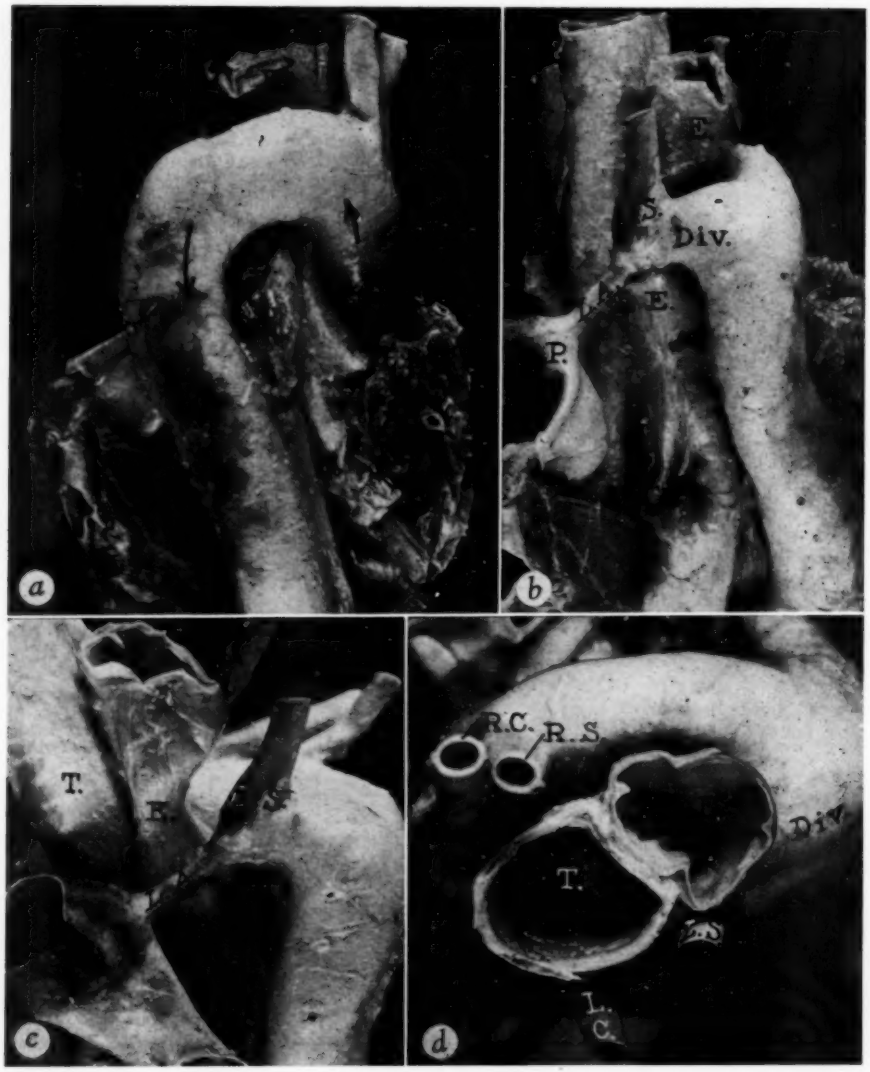

Fig. 4.—*a*, Mediastinal structures viewed from behind. The right aortic arch (arrow up) passes behind the esophagus (*E.*) to reach the left side of the body and join the descending aorta (arrow down). *b*, Mediastinal structures viewed from the left. The right aortic arch passes behind the esophagus and joins the descending aorta. At the junction of the two structures is a diverticulum (*Div.*) from which the left subclavian artery (*L.S.*) and the ligamentum arteriosum (*L.A.*) arise. The lower end of the ligamentum is attached to the left pulmonary artery (*L.P.*). The esophagus is compressed by the vascular ring. *c*, Same perspective as *b* but with aorta retracted posteriorly to show the severe compression of the esophagus from behind forward. *d*, Trachea and esophagus viewed from above. The esophageal lumen is compromised by the retroesophageal segment of the right aortic arch pressing against the posterior wall of the esophagus. The abbreviations are as in the other illustrations.

COMMENT

This patient had experienced symptoms associated with a congenital anomaly of the aortic-arch system since early childhood. Her lifetime was marked by constant apprehension, choking, and dyspnea. It is of interest that her mother had a congenital anomaly of the esophagus and hiatal herniation that contributed to the mother's death. Despite severe esophageal and tracheal compression, the patient lived to the age of 62 years, but her last 2 years were complicated by drug addiction and invalidism.

Surgical treatment, consisting of severance of the ductus arteriosus, at an early age would probably have alleviated the compression caused by the vascular ring. When the diagnosis of vascular ring finally was established, the patient was 54 years of age and had signs of congestive cardiac failure.

The presence of a congenital anomaly of the aortic-arch system in an elderly person is of interest from a diagnostic viewpoint. As in most cases of vascular ring, the diagnosis can be established by correlation of the history with relatively simple diagnostic studies, such as roentgenographic examination of the esophagus. Although such anomalies are not common in middle-aged or elderly persons, the presence of symptomatic congenital vascular rings must be considered when the history includes symptoms commonly associated with these anomalies.

The malformation of the aortic-arch system present in this case represents the commonest variety of significant anomalies of the system.[1] One may view the genesis of the anomaly, as it was observed in this case, as representing a modification of a double aortic arch with a left-sided ductus arteriosus; if in such an aortic-arch system there is interruption of the left arch between the origins of the left common carotid and left subclavian arteries, the malformation present in this case would result. The diverticulum from which the left subclavian artery arose and into which the ligamentum arteriosum inserted may be considered as the posterior remnant of a left aortic arch.

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Supravalvular Stenosing Ring of the Left Atrium

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During the period of infancy and childhood, obstruction to the emptying of the left atrium is unusual and may be caused by any of several malformations. Rheumatic mitral stenosis of physiologic significance is infrequently found during this age period.[1] Other causes include mitral stenosis secondary to endocardial fibroelastosis,[2] congenital mitral stenosis,[3] cor triatriatum,[4] and infradiaphragmatic total anomalous pulmonary return.[5] The purpose of the present communication is to draw attention to another cause of left atrial obstruction, namely, a supravalvular stenosing ring. In these cases a small, shelf-like ring with a narrow orifice occurs slightly above the annulus of the mitral valve. No true third chamber is present as in cor triatriatum, and the mitral valve may be normally formed. Only 5 cases of supravalvular stenosing rings have been reported in the literature, three rather sketchily. We are reporting one autopsied case in which this lesion was not diagnosed either clinically or during intracardiac surgery for an associated ventricular septal defect. In addition, we have seen two patients who had simultaneous correction of ventricular septal defects and congenital mitral stenosis whom we now believe had supravalvular stenosing rings. None of these cases was diagnosed clinically, and in the one case which came to autopsy, the significance of the ring was not appreciated at the time of the original examination of the heart.

CASE REPORT

CASE 1.—R.S. was the product of a normal pregnancy, complicated only by an infection of the urinary tract in the first trimester. Delivery was normal, and the baby weighed 5 pounds, 15½ ounces at birth. Two pediatricians examined this child shortly after birth, and she was considered to be normal. At 1 month of age, the child was admitted to a local hospital with the diagnosis of pneumonia. She responded poorly to antibiotics and was subsequently diagnosed as having congenital heart disease, tentatively diagnosed as an ostium primum defect. She was given digitalis and discharged after recovery from this acute episode.

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The child was first seen at the University of Minnesota Hospitals at the age of 4 months. She had been free of respiratory difficulties since her previous hospitalization but was a very slow eater and weighed only 7 pounds, 4½ ounces.

Physical examination revealed questionable cyanosis of the lips, slight intercostal retractions, and a loud systolic murmur over the precordium. No thrill was palpated. The femoral arteries were readily palpable. Cardiac fluoroscopy revealed a moderate pectus excavatum deformity. The heart was considered to be moderately enlarged with biventricular prominence (Fig. 1). At fluoroscopy, the left atrium appeared enlarged. There was a distinct increase in the pulmonary vasculature. Electrocardiogram revealed left axis deviation, horizontal heart, incomplete right bundle branch block, prolonged P-R interval, peaked P waves, and right ventricular hypertrophy, and was considered to be consistent with the diagnosis of ostium primum syndrome.

The child was admitted to the hospital on May 5, 1957, for cardiac catheterization (Table I). This revealed an obvious left-to-right shunt at the ventricular level with an increase in the oxygen content of 4 volumes per cent, and also showed pulmonary hypertension of 85/50 mm. Hg. The femoral artery desaturation of 86 per cent indicated that there was also a right-to-left shunt, and suggested the possibilities of a single ventricle with a bidirectional shunt, a large ventricular septal defect, or a common truncus arteriosus.

TABLE I. RIGHT HEART CATHETERIZATION FINDINGS (CASE 1)

	AGE 5 MONTHS		AGE 2 YEARS	
	PRESSURES (MM. Hg)	O_2 CONTENT (VOL. %)	PRESSURES (MM. Hg)	O_2 CONTENT (VOL. %)
IVC	—	6.0	—	9.8
SVC	—	7.2	—	—
RA	12/4 m 7	8.0	—	9.5
RV	85/0	12.0	125/0	17.1
PA	85/50 m 70	12.1	—	—
Femoral artery	—	13.4 (86.4%)	—	18.0 (96.9%)
Corrected capacity	—	15.6	—	18.3

On May 13, 1957 the patient was admitted to the hospital for the second time and an angiocardiogram was made. This revealed that the contrast medium entered the right atrium and then the right ventricle via the inferior vena cava. Subsequent films showed filling of the pulmonary artery, where the contrast media appeared to be diluted, presumably by a left-to-right shunt, and the presence of two ventricles. The relationship of the great vessels was normal. There was a large left atrium, with prolonged delay in emptying of this chamber (Fig. 2). The diagnosis on this basis was ventricular septal defect.

At 1 year of age she was again seen for cardiac re-evaluation. At that time she was doing fairly well but her weight was only 10 pounds, 6 ounces, and her height was 25 inches. Physical findings were unchanged, except that a diastolic murmur at the apex was heard by one examiner. Roentgenograms were taken and the previous angiocardiogram was reviewed at this time, and the question of a corrected transposition with a ventricular septal defect was raised.

On Jan. 4, 1959, the child was readmitted to the University of Minnesota Hospitals, where cardiac catheterization was carried out and a selective angiocardiogram was made (Table I). The femoral arterial sample was taken first and was fully saturated, indicating no appreciable right-to-left shunt. The data also indicated a large left-to-right shunt at the ventricular level. The pulmonary artery could not be entered, but the right ventricular pressure had increased to 125/0 mm. Hg. The selective angiocardiogram showed no evidence of a right-to-left shunt and normally located great vessels, and the final diagnosis was ventricular septal defect. Bone age was also examined at this time and was found to be retarded. Because of her poor gain in weight and the large left-to-right shunt indicated by the catheterization, the patient was scheduled for a corrective operation.

Accordingly, the patient entered the University of Minnesota Hospitals for the fourth time on Feb. 4, 1959, at the age of 2 years. Physical examination revealed a harsh Grade 4 systolic murmur which was loudest at the apex. The second pulmonic sound was very strikingly increased over the second aortic sound and was widely split. No diastolic murmur was heard.

Laboratory data at this time revealed a hemoglobin of 13.4 Gm., normal white blood cell count and differential, normal urinalysis, normal bleeding, clotting, and prothrombin times, and a platelet count of 508,000. Platelet count was repeated 4 days later and was 203,000. An electrocardiogram revealed no essential changes from previous tracings (Fig. 3).

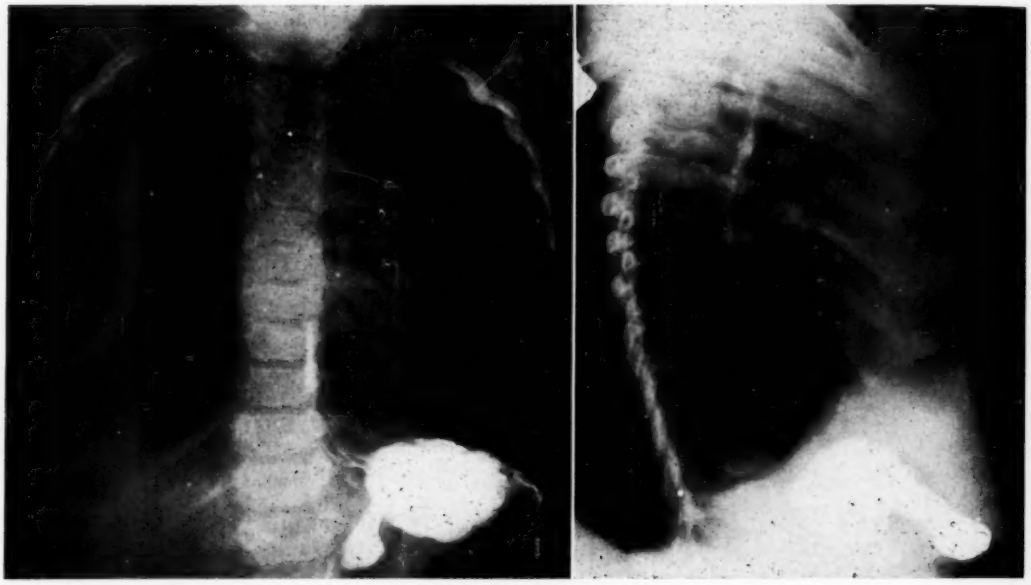

Fig. 1.—Posterior-anterior and lateral views of the chest, Case 1, taken when the child was 20 months old. Enlargement of the left atrium as well as of both ventricles may be seen. Pulmonary vasculature is distinctly increased.

On the fifth hospital day the child was taken to surgery and connected to the pump-oxygenator. A ventricular septal defect which measured approximately 2 cm. in diameter was found. Direct manometric measurement of the pressure in the pulmonary artery with the thorax open was 75/30 mm. Hg, and in the aorta, 93/70 mm. Hg. The defect was closed with an Ivalon patch. The total time on the pump was 35 minutes. Blood chemistries drawn immediately after surgery showed: carbon dioxide, 17; chloride, 100; sodium, 141; potassium, 4.0. Four hours postoperatively, she was doing well except for a slightly low urine output. Seven hours postoperatively, the patient appeared listless, slightly cyanotic, and all four limbs were in flexion spasm, that is, with both fists clenched and with bilateral plantar flexion. Poor breath sounds were heard on the left; the pulse and heart rate were 160, regular and strong. The Anesthesia Service was called and the patient was suctioned. The material aspirated was thought to be slightly bile stained. The patient improved slightly on artificial respiration with bag oxygen, but all voluntary respirations had ceased. The heart sounds appeared weaker and a few extrasystoles appeared, followed very quickly by asystole. In spite of intracardiac adrenaline and cardiac massage, the patient expired and was pronounced dead 7 hours and 45 minutes after the operation.

Autopsy.—The body was that of a poorly developed, poorly nourished white girl, measuring 75 cm. in length and weighing 6.9 kilograms. The face and upper thorax were markedly cyanotic and the fingernail beds were mildly cyanotic. There was a very sharp point of demarcation of the cyanosis over the upper thorax.

The heart appeared to be moderately enlarged and, with the lungs, weighed 208 grams. The epicardium, myocardium, and endocardium were normal in color and consistency except for a few small hemorrhages. The thickness of the left ventricle was 6 mm., and that of the right ventricle was 9 mm. The valve leaflets showed no thickening or deformities. The tricuspid valve measured 6 cm. in circumference, and the mitral valve, 3.5 cm. The aorta was right-sided both in the arch and the descending thoracic portion, and had three branches at its arch. The left subclavian artery came off the aorta 2 cm. below the right subclavian and passed behind the trachea and eosphagus, but examination of the interior of the latter organs revealed no evidence of compression. The ventricular septal defect measured 12 mm. in diameter, and the Ivalon patch covered the opening very snugly, with only one probe-patent area. Both the right and left atria were enlarged and the left atrium was remarkably thickened. There was a small, smooth-edged, thin, shelf-like formation at the bottom of the left atrium, a few millimeters above the mitral valve. The atrial appendage was above this shelf (Fig. 4).

The autopsy was conducted with particular reference to possible air emboli, but no evidence was found for embolization. The remainder of the autopsy, including a postmortem blood culture, was normal.

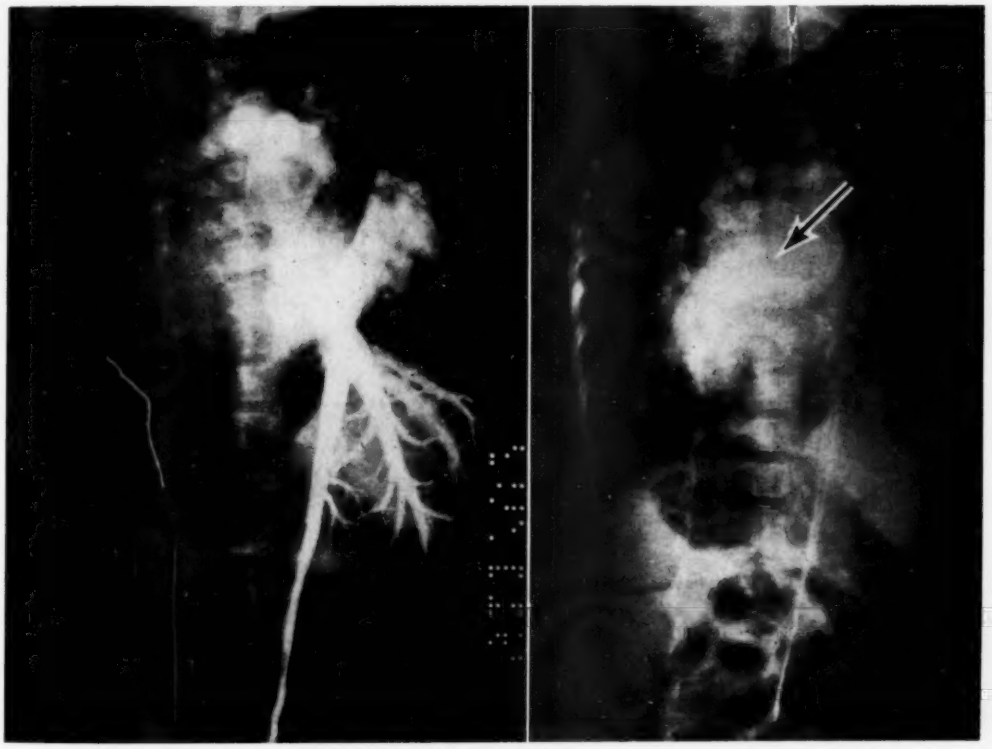

Fig. 2.—Angiocardiographic study of Case 1 made when the child was 5 months of age. The film on the right, taken 1.8 seconds after the one on the left, demonstrates a heavy concentration of dye in the left atrium (*arrow*) that persisted on several films.

Microscopic Findings.—Sections taken through the mitral valve and the supravalvular ring demonstrated a high degree of organization of the ring (Fig. 5). The ring was composed of collagenous fibers, which appeared to originate within the substance of the atrium. A few small blood vessels traversed the ring. The wall of the atrium was thick and the endocardium was markedly thickened in a manner consistent with endocardial fibroelastosis. No other areas of endocardial fibroelastosis were found in the rest of the heart. There were numerous areas of hemorrhagic damage in the myocardium, thought to be the result of cardiac massage.

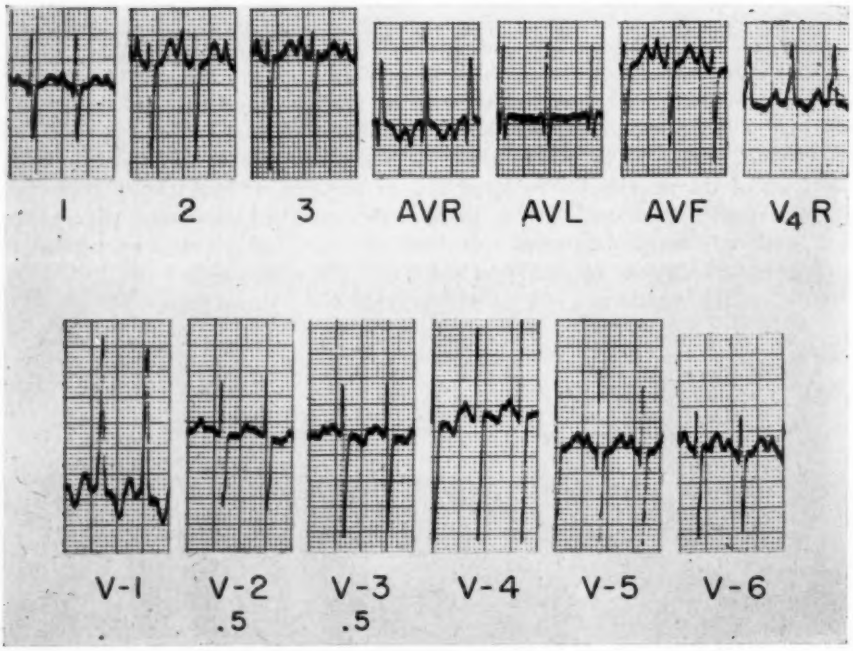

Fig. 3.—Electrocardiogram of Case 1 taken when the child was 2 years old. This tracing, essentially similar to tracings recorded at earlier ages, revealed left axis deviation, horizontal heart, prolonged P-R interval, peaked P waves, and right ventricular hypertrophy.

Fig. 4.—Autopsy specimen of Case 1. The white marker is holding apart the walls of the thickened fibroelastotic left atrium. The ring may be seen just above the mitral valve. Note also the ventricular septal defect and the snug-fitting Ivalon patch.

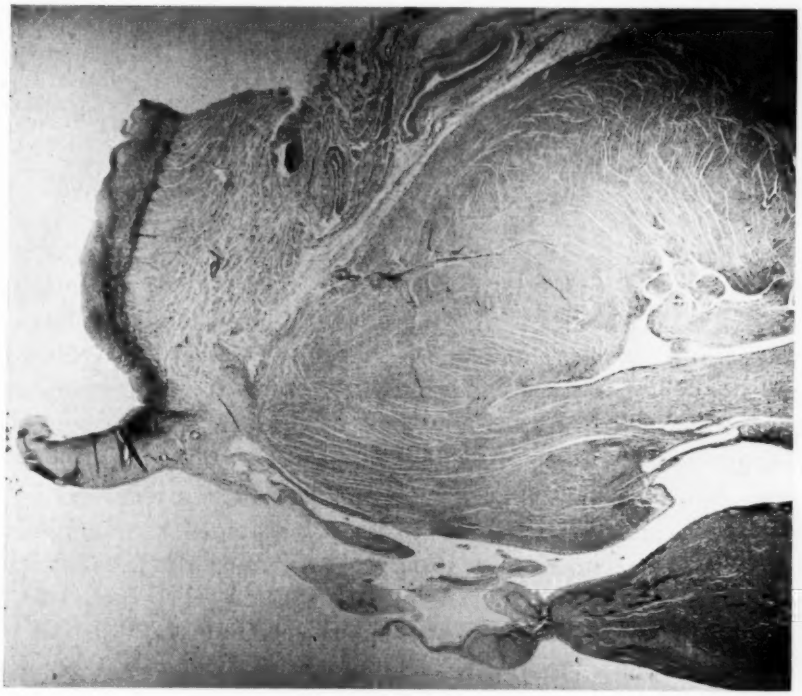

Fig. 5.—Low-power view of a section taken through the supravalvular ring. The left ventricle is at the right, with portions of the mitral valve beneath. The left atrium has been folded back on the left ventricle during the fixing process.

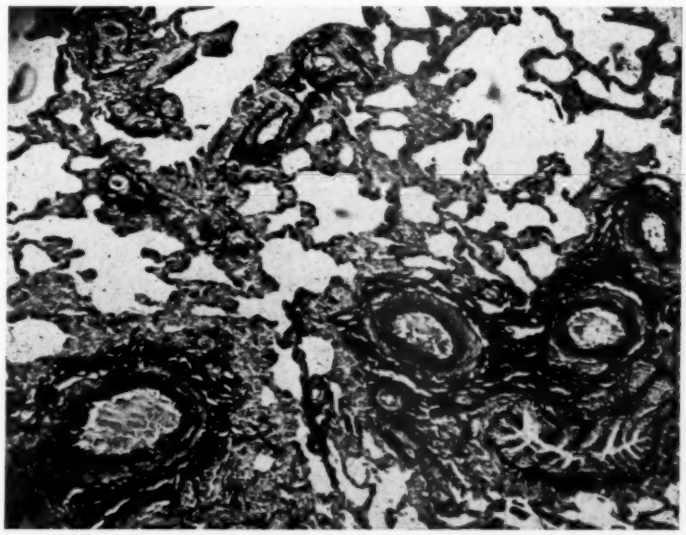

Fig. 6.—Section of the lungs (Case 1) demonstrating an increase in the number of blood vessels, marked medial hypertrophy, and the occlusion of small arterioles by intimal proliferation.

The media of the pulmonary arteries was markedly thickened. Intimal proliferation was generally less striking, but a number of the smaller arterioles were nearly completely occluded. The number of vessels per unit area was also considerably increased. The pulmonary veins were large, dilated, and thickened (Fig. 6). Scattered areas of patchy atelectasis were also seen.

Sections of kidney, adrenal, pancreas, spleen, liver, thymus, diaphragm, and ribs were within normal histologic limits.

DISCUSSION

The case reported by Rogers and co-workers[6] was an 8-month-old girl who died in heart failure after a brief febrile illness. Endocardial fibroelastosis of the posteromedial wall of the left ventricle was found and thought to have produced shortening of the chordae tendineae of the mitral valve, with resultant mitral insufficiency. A shelf-like ring protruding 3 mm. into the left atrium and having an orifice 6 mm. in diameter was found above the mitral valve. Rogers postulated that this ring was a reaction to the trauma of the regurgitant streams of blood.

Another case of a similar malformation was briefly recorded in the same article, and is presumably the same as Case 3 reported by Helmholz.[7] In this 3-year-old girl the 2.5 cm. ring was found above the left atrioventricular valve in combination with probable insufficiency of this valve, corrected transposition of the great vessels, and a patent ductus arteriosus. This child died of pulmonary edema. The Mayo Clinic group[7] has also reported a third case, that of a 13-year-old boy who died after surgical closure of a ventricular septal defect. Pathologically, in addition to the repaired ventricular septal defect, the heart showed corrected transposition of the great vessels, a large left atrium with hypertrophied wall, and short chordae of the septal and posterior leaflets of the left atrioventricular valve. The orifice of the stenosing ring measured about 2.5 cm.

Kipkie and Johnson,[8] in an article concerned primarily with two cases of associated glomerulonephritis and periarteritis nodosa, briefly recorded the presence of a supravalvular ring in one of these cases. This was in an 11-year-old boy who died of what appeared to be a combination of renal and cardiac failure. At autopsy, the heart was found to have a large, high ventricular septal defect, an overriding aorta, and right ventricular hypertrophy. A narrow band of connective tissue which measured 1 to 2 mm. in width and 1 mm. in thickness was found running in a circumferential manner above the mitral valve.

A fifth case, reported by Johnson and Dodd,[9] occurred in an 11-year-old girl who died with anasarca, apparently the result of glomerulonephritis and heart failure. Autopsy revealed a patent ductus, 8 mm. in diameter, and a fibrous ring encircling the left atrium about 4 mm. above the mitral valve. This ring resulted in an orifice only 1 cm. in diameter. Shortening of the chordae tendineae, with slight rolling of the edge of the mitral valve, was also found. Severe intimal thickenings and increased collagen in the media of many of the smaller arteries was seen in the lungs, as well as in the liver, spleen, adrenals, and pancreas. These lesions, together with the pathology of the mitral valve, were thought to be suggestive of periarteritis nodosa, rheumatic fever, or possibly another collagen disease. The ring itself was considered to be either secondary to regurgitant jet or congenital in origin.

TABLE II. SUMMARY OF CASES OF SUPRAVALVULAR STENOSING RING OF THE LEFT ATRIUM

	SEX	AGE (YR.)	CONGESTIVE FAILURE	SYSTOLIC MURMUR	DIASTOLIC MURMUR	THRILL	PULMONIC SECOND SOUND	X-RAYS	ECG	MITRAL VALVE	OTHER CONGENITAL HEART DEFECTS	REMARKS
Case 1	F	2	0	LLSB	?	LLSB	Accentuated	Cardiomegaly. PVE	LAD, IRBBB, RVH	Normal	VSD	Died 8 hr. after repair of VSD
Case 2	M	3*	0	4LIS	Early	4LIS	Slightly accentuated	Cardiomegaly. PVE	NAD, RVH, IRBBB	Normal	VSD	Successful repair of both lesions. PA pressure preop., 50/18; wedge pressure, 15 mm. Hg
Case 3	M	3*	Yes	LLSB	0	LLSB	Accentuated	Cardiomegaly. PVE	RAD, CVH, IRBBB	Normal	VSD	Successful repair of both lesions. PA pressure preop., 85/49 mm. Hg
Rogers[6] (Case 1)	F	8mo.	Terminally	Mitral	0	0	Accentuated	Marked cardiomegaly	RAD, RVH	Insufficient	Bicuspid aortic valve	Endocardial fibroelastosis of left ventricle
Rogers[6] (Case 2)	F	3	Terminally	—	—	—	—	—	—	Insufficient	Corrected transposition and PDA	Presumably same as Case 3 of Helmholz[7]
Helmholz[7]	M	13	0	—	—	—	—	—	—	Insufficient	Corrected transposition and VSD	Died following repair of VSD
Kipkie[8]	M	11	Terminally	—	—	—	—	—	Marked RAD	Normal	Eisenmenger's complex	Periarteritis nodosa and glomerulonephritis
Johnson[9]	F	11	Terminally	Base and mitral	Mitral and apex	Apex	Accentuated	Marked cardiomegaly	RVH	Insufficient	Patent ductus	Periarteritis nodosa and glomerulonephritis

*Age at operation.

LLSB: Left lower sternal border. PVE: Pulmonary vascular engorgement. LAD, RAD, NAD: Left, right, and normal axis deviation. IRBBB: Incomplete right bundle branch block. VSD: Ventricular septal defect. PDA: Patent ductus arteriosus.

As mentioned earlier, two additional patients have been seen at the University of Minnesota Hospitals who probably had a supravalvular stenosing ring (Table II). Both of these children underwent open-heart surgery using a pump-oxygenator for ventricular septal defects. During operation, an additional lesion of the left heart was suspected because of a huge left atrium, elevated left atrial pressures, and a thrill in the mitral area. In both cases, a mitral commissurotomy was performed but the mitral valve leaflets appeared to be entirely normal after the "valvuloplasty," in contrast to the deformed leaflets seen in rheumatic[1] or congenital mitral stenosis.[3] After operation, both of these children had uneventful recoveries.

An expanded version of Table II has failed to yield any obvious clues to clinical diagnosis. At the present time, we are unable to differentiate these cases clinically from those of isolated ventricular septal defects with elevated pulmonary arterial pressures. One of our three cases showed broad notched P waves in the electrocardiogram (Case 3), but this has been a finding in 15 per cent of the cases of isolated ventricular septal defects.[10] Measurement of pulmonary arterial wedge pressure was made in only one of these patients (Case 2) and was found to be only minimally elevated, 15 mm. Hg. as compared to the normal range of 5 to 13 mm.Hg.[11,12] In retrospect, the only feature that might aid in reaching the correct diagnosis was the markedly delayed emptying time of the left atrium noted in the angiocardiographic studies of the first case.

We feel that the supravalvular stenosing ring accounted for the failure of the first child to survive operation. Our failure to diagnose and to correct all of the cardiac malformations at the time of the operation seems to be the most reasonable explanation for this child's unfortunate death. In the light of our present knowledge, antemortem diagnosis can best be made at the time of surgical operation by looking for signs of left atrial obstruction, particularly direct measurement of left atrial pressures.

Although in four of the five cases reported in the literature there was associated mitral insufficiency, this was not found in any of the cases in the present series. We believe that supravalvular stenosing rings are of congenital origin. It seems unlikely that a regurgitant localized jet of blood could produce a smooth-edged symmetrical ring, even when redirected by a cusp-like formation of the original jet lesion.[9,13] Furthermore, the likelihood of a congenital origin is enhanced by the fact that all eight cases had other congenital cardiac anomalies.

Two of these children also had a severe generalized disease of the arteries as well as terminal glomerulonephritis. It will be of interest to observe future cases of supravalvular stenosing rings for further association between these seemingly unrelated pathologic entities.

SUMMARY

One autopsied case and two probable clinical cases of supravalvular stenosing ring of the left atrium have been added to the five cases previously reported in the literature. Detailed examination of the records of these patients and a review of the literature has brought to light only one possible diagnostic clue, namely, delayed emptying of the left atrium on angiocardiographic study.

It is hoped that this paper will encourage surgeons to look for possible left atrial obstruction at the time of repairing other congenital cardiac lesions. Although these rings are undoubtedly uncommon, the possibility for surgical repair warrants a careful examination of the left atrium at the time of surgery.

We are indebted to Dr. James R. Dawson, Jr., of the Department of Pathology, for his review of the pathologic findings of the first case and for his many helpful comments.

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Review

Diagnostic Contribution of the Vectorcardiogram in Hemodynamic Overloading of the Heart

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This paper represents a review of the concepts developed during the last five years in the Laboratory of Vectorcardiography of the Mexican Institute of Cardiology. We shall divide the paper into two complementary parts: the first one is devoted to the vectorcardiographic consequences of hemodynamic overloadings, and the second one, to the diagnostic value of the vectorcardiogram (VCG) in relation to hemodynamic overloadings. These two parts are not identical. They correspond to the *electrogenic* and *diagnostic* aspects of clinical vectorcardiography as we have defined them elsewhere.[8] One is the reciprocal of the other, and both are mutually complementary. The electrogenic knowledge will serve only as a basis for the diagnostic interpretation of the VCG but is not to be equated with this interpretation. Besides the electrogenic factors connected with overloading of the ventricles, several other factors have to be taken into consideration for the diagnosis, such as the age and sex of the patient, the contour of the P loop, the evidence of intraventricular conduction defects, the signs of myocardial injury or ischemia, etc.

ELECTROGENESIS

A. *General Factors.*—Let us remember that the work performed by any machine is equal to a certain mass times the energy gain of that mass, and, also, that the gravitational and kinetic energies can be disregarded in comparison to the pressure energy for the particular case of the heart. This means that the work performed by the heart as a pump would be equivalent to the mass of blood ejected times the mean pressure of the corresponding arterial vessel. Consequently, any increase in heart work, i.e., any ventricular overloading, could be due to an increase in the volume of blood per beat (volume overloading or diastolic overloading) or to an increase in the mean arterial pressure (pressure overloading or systolic overloading).

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There is a general agreement that ventricular overloading of one ventricle gives rise to increased voltage and delayed manifestation of QRS vectors, whereas the repolarization changes are spatially opposite to the QRS changes. This agreement is in sharp contrast to the lack of uniformity concerning the mechanism of production of such alterations.[28,32] In spite of this, it can be accepted that ventricular overloading induces a displacement of the R loop* of the VCG in a direction coincident with the spatial orientation of the affected free ventricular wall: thus, backward, to the left, and slightly upward in left ventricular overloading (LVO), and forward, to the right, and downward in right ventricular overloading (RVO). For some reason which is not evident to us, most patients with pulmonary, and some with congenital, heart disease with RVO show significant upward displacement of the S loop. This has been attributed to forces generated by the "crista supraventricularis," or the so-called "ceiling" of the right ventricle.[27,35] As for the repolarization effects, the junction between the QRS and T loops (J point), as well as the center of gravity of the T loop, are usually displaced in a direction opposite to that of the QRS-loop changes, that is, forward and to the right in LVO, and backward, to the left, and upward in RVO.

The Q-loop alterations are usually opposite and proportional to, although less important than, the R-loop changes. These concomitant alterations of the Q and R loops were formerly considered to be the result of positional changes[1,2,21,23] due to clockwise or counterclockwise rotation of the heart on its anatomic axis. But, because these rotations have not been confirmed at autopsy,[24] there has been a recent tendency to attribute them to intrinsic alterations of depolarization[2,17,24] rather than to extrinsic, positional changes: the opposition and proportionality between the Q- and R-loop changes could be due to the *simultaneous* hypertrophy of the septal and free walls. Thus, because the normal Q loop of the VCG is due to an early preponderance of the left septal activation, we would expect it to increase in LVO and decrease in RVO. This is indeed the case with significant volume overloading of the left ventricle[8,11] and with severe overloading of the right ventricle.[8,20] But a LVO which is complicated by chronic coronary insufficiency,[7] such as that seen in arterial hypertension, aortic stenosis, syphilitic aortic insufficiency, and coarctation of the aorta, may show a reduction of the Q loop. This reduction of the Q loop has been attributed to incomplete left bundle branch block,[32] to left septal myocardial sclerosis,[7] or to early preponderance of the vectors of the left free wall.[7]

In regard to the electrogenic influence of volume or pressure overloadings, it should be noted[8,10,14] that the type of overloading—not only the side which is overloaded—modifies the electrical field of the heart, although we do not know the exact mechanism of this electrogenic process. Thus, in systolic overloading of the right ventricle (SO of RV) there is a progressive preponderance of the vectors of the right septal and free walls, and apparent reduction of the corre-

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***For the sake of description, we shall call "Q loop" the initial loop of ventricular depolarization when it is inscribed anteriorly and with a counterclockwise rotation in the horizontal plane; "R loop," the intermediate loop of depolarization, oriented to the left; "S loop," the terminal loop of depolarization, oriented to the right.**

sponding left vectors without significant slurring of the QRS loop. On the contrary, in diastolic overloading of the right ventricle (DO of RV), the increased vectors of the right free wall are accompanied by a late slurring of the QRS loop (delayed development of the corresponding instantaneous vectors) without any apparent reduction of the vectors of the left septal and free walls. In systolic overloading of the left ventricle (SO of LV), the increased vectors of the left free wall are accompanied by reduced left septal vectors, so that the center of gravity of the QRS loop is significantly displaced backwardly and to the left, and thus gives rise to important "secondary" changes of the repolarization loop, the center of gravity of which becomes displaced forward and to the right. In diastolic overloading of the left ventricle (DO of LV) the increased vectors of the left free wall are accompanied by an opposite increase in the left septal vectors, so that the center of gravity of the QRS loop is little modified, and the "secondary" changes of the repolarization loop are almost inapparent.* The contrast between the important T-loop changes in SO (negative T waves in the left precordial leads) and the "normal" T loop of DO (positive, symmetrical T waves in the left precordial leads) might be dependent on the frequent coronary complications,[7] high oxygen comsumption,[26] and metabolic disturbances of cardiac muscle[38] found in SO of LV.

It is important to recall here that the VCG represents the vectorial resultant of several simultaneous electromotive forces, and that, therefore, the patterns of overloading are determined by the hemodynamic role of both ventricles. Now, although it is generally agreed that overloading of one ventricle may preclude the identification of that of the other, we feel that too little attention has been paid to the fact that *underloading* of one ventricle may exaggerate the *apparent overloading* of the other. For example, in cases of tricuspid atresia, there is a DO of LV accompanied by a nonfunctioning right ventricle, and the VCG (with less than 100 per cent DO of LV) is comparable to that in cases of patent ductus arteriosus, wherein the DO of LV is three or more times the normal (Fig. 3; see also Wenger,[36] page 145, and Duchosal,[17] page 178). This means that comparable effects upon the VCG are produced by uneven situations of the LV because of a SO of RV in cases of patent ductus arteriosus and an underloading of the RV in cases of tricuspid atresia. An example of LV *underloading* is found in cases with RVO in which high pulmonary resistances or significant V-A shunts interfere with the diastolic filling of the left ventricle. This occurs in cases of Fallot's tetralogy, severe mitral or pulmonary stenosis, and severe pulmonary hypertension, in which the systemic output has fallen. In all of these cases the left ventricular loops (Q and R loops) are importantly reduced or even absent on the VCG,[15,20,25] so that the center of gravity of the QRS loop shows an extreme rightward displacement and the tip of the S loop in the horizontal plane may show a counterclockwise rotation. We feel that this type of tracing is the result of an extreme preponderance of the RV due to a volume underloading of the left ventricle.

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*In extreme DO of LV, a larger amount of blood is pumped out of the ventricle in the usual interval of time, and this requires an increased ejection pressure. The consequence is a superimposed systolic overloading of the LV,[37] with VCG changes which correspond to this type of overloading, not to a diastolic overloading.[8]

Finally, it should be borne in mind that a homolateral superimposed bundle branch block is a frequent finding in ventricular overloadings.[29] The VCG is then modified in such a way that peculiar diagnostic problems arise. On the one hand, the usual coincidence of right bundle branch block (RBBB) with RVO, as well as the coincidence of left bundle branch block (LBBB) with LVO, make uncertain the diagnosis of either the loading or the block. On the other hand, the recognition of both the block and the overloading may greatly contribute to the hemodynamic and nosologic orientation of the diagnosis,[3] as we shall see in the last part of this paper.

B. *Electrogenesis in Different Entities.*—The presentation of our material will be divided into two main groups: congenital and acquired heart diseases. In each group, only the cases in which the diagnosis was reasonably reliable were included, and those with technically unsatisfactory tracings were excluded. For the recording of our tracings, we used a DuMont Dual Beam oscilloscope. The frontal and horizontal loops were recorded simultaneously, then enlarged photographically, analyzed, and redrawn at a known amplification. We used Grishman's cube method, always with low and high sensitivity, and, for each sensitivity, the recording was always made without time markings as well as with 1/200 and 1/500-second interruptions. We consider these details to be indispensable for the correct analysis of the loops. For the spatial calculus of the different vectors, we used the formula $S_V = \sqrt{x^2 + y^2 + z^2}$, where S_V is the spatial vector, and x, y, z represent the transverse, vertical, and sagittal components of that vector. We calculated the spatial magnitude of the initial, intermediate, and terminal maxima of the QRS loop, which usually correspond to the apex of the Q, R, and S loops, respectively (cf. footnote on page 297). The sequence of presentation of our findings will be: left ventricular overloadings, right ventricular overloadings, and biventricular overloadings.

1. *Congenital Heart Disease.*—

Aortic stenosis (SO of LV with early coronary insufficiency): 10 cases with basal systolic murmur and thrill propagated to neck vessels (5 cases confirmed by catheterization of the left heart); 17 to 27 years old (mean age, 20 years). There was infrequent QRS enlargement: in 8 cases <90 msec.; 1 case, 105 msec.; 1 case, 120 msec. There was counterclockwise (C-CW) rotation in the horizontal plane in all cases, except in one in which there was complete LBBB. C-CW rotation in the frontal plane was found in only 4 cases. Reduction of the Q loop was obvious (10 cases <0.15 mv.; 7 cases <0.10 mv.). There was no enlargement of the R loop (9 cases <1.0 mv.): the only exception was a case in which there was a complete LBBB. There was terminal slurring similar to that of coarctation of the aorta in 5 cases.

Coarctation of the aorta (SO of LV with early coronary insufficiency): 19 cases proved surgically; 5 to 42 years old (mean age, 22 years). There was some tendency to QRS enlargement: 6 cases ≥90 msec.; 13 cases ≥80 msec.; mean duration, 82 msec. C-CW rotation of QRS_H was found in all 19 cases, but only in 6 cases for QRS_F. The Q loop was absent (2 cases) or definitely reduced (13 cases <0.15 mv.). The R loop was enlarged (19 cases >1.0 mv.; 5 cases >1.5 mv.). There was infrequent delay of the R-loop apex (3 cases ≥40 msec.). There was terminal slurring of QRS in 11 cases, most of them with small terminal "appendage."

Tricuspid atresia (DO of LV with nonfunctioning RV): 5 cases proved by catheterization and surgery, having cyanosis and left axis deviation; age ranged from 1 to 15 years (mean age, 9 years). QRS duration was 90 msec. in 2 cases. There was C-CW rotation of QRS_F in 2 cases, and figure-of-eight rotation in 3 cases. QRS_H was rotated *clockwise* in 4 cases without obvious signs of LBBB (Q loop present and even enlarged; intermediate "plateau" of the R loop absent; QRS

duration <90 msec.). The Q loop was enlarged (5 cases >0.2 mv.; 3 cases >0.6 mv.), as was the R loop (4 cases >1.0 mv.; 3 cases >2.5 mv.). There was frequent delay of the R-loop apex (3 cases ≥40 msec.). The R loop was significantly displaced backward, upward, and to the left (mean direction of R_F was −24°; that of R_H was −46°).

Atrial septal defect (DO of RV proportional to A-V shunt; SO of RV when pulmonary hypertension is present): 39 cases proved by catheterization; 9 to 57 years old (mean age, 24 years). The QRS interval was usually prlonged (30 of 39 cases ≥90 msec., with mean value of 93 msec.). There was bizarre rotation of the QRS loop because of independent variability of R and S loops (see below). The Q loop may be normal (15 of 39 cases), reduced (18 of 39 cases <0.15 mv.), or absent (6 of 39 cases). When the Q loop was absent, the VCG started to the left and slightly posteriorly, and important pulmonary hypertension was usually present (4 of 5 cases >50 mm. Hg; mean systolic pressure, 80 mm. Hg). The R loop had no slurrings and usually (27 of 39 cases) was of normal voltage (0.7 mv. ≤R ≤1.2 mv.; mean voltage, 0.82 mv.) but was reduced in cases with important pulmonary hypertension (mean voltage of 0.61 mv.). There was variable rotation of R_H (C-CW in 20 cases; CW in 19 cases), but frequent CW rotation of R_F (31 cases). When R_H was CW, R_F was also CW (19 of 19 cases); when R_H was C-CW, R_F might still be CW (11 of 20 cases). The S loop was usually prominent (32 cases ≥0.5 mv.; mean voltage, 0.8 mv.) and slurred (31 cases). Slurring was either terminal (20 of 31 cases) or preterminal (11 of 31 cases); it was almost constant when QRS ≥90 msec. (29 of 30 cases); it was of reduced extension when QRS <90 msec. (2 of 9 cases). The S/R quotient was significantly increased (mean value, 0.95). There was C-CW rotation of S_H (7 of 11 cases) when slurring was preterminal, but usually CW (15 of 20 cases) when slurring was terminal. If we consider as evidence of RBBB a VCG with a late "appendage" pointing froward and to the right,* RBBB was present in 25 of 39 cases; all of these cases had a QRS duration of ≥90 msec.

Tetralogy of Fallot (SO of RV of "fixed" systemic value; diastolic *underloading* of LV proportional to V-A shunt): 17 cases proved by catheterization, 6 of which were confirmed at autopsy; age ranged from 9 months to 20 years (mean age, 5 years). QRS duration was usually normal (12 cases <90 msec.; mean duration, 70 msec.). CW rotation of QRS_F and QRS_H was almost constant (15 cases); only 2 cases had figure-of-eight rotation of QRS_F, one with CW rotation of QRS_H and the other with figure-of-eight rotation of QRS_H. There was reduced voltage of the Q loop (15 cases <0.15 mv.) as well as of the R loop (16 cases <1.0 mv.; 13 of the 17 cases <0.5 mv.; mean voltage, 0.35 mv.). The S loop was prominent, so that the S/R quotient was increased (16 cases >1.0; 11 of the 17 cases >3.0), but terminal slurring was unusual (4 of 17 cases) and inconspicuous. The combination of small Q and R loops with neat (rapid and uniform) and prominent S loop gave rise to a stereotype in 12 cases, completely different from that of atrial septal defect.

Fallot's trilogy (SO of RV; DO of RV when A-V shunt is present; relative DO of LV when V-A shunt is present): 9 cases proved by catheterization, 7 of which were confirmed during operation; age ranged from 4 to 32 years (mean age, 12 years). QRS duration was variable (4 cases ≥90 msec.; mean value, 76 msec.). There was CW rotation of QRS_F and QRS_H in all cases. The Q loop was usually absent (5 cases) or small (1 case <0.15 mv.). When absent, the VCG started dorsal and leftward, and the mean systolic pulmonary pressure was 143 mm. Hg (it was 65 mm. Hg when Q was of normal voltage). The R loop was usually reduced (9 cases <1.0 mv.; 2 of 9 cases <0.5 mv.). The S loop was prominent, so that the S/R was high (8 cases >1.0; 4 of 9 cases >3); the only case without a prominent S loop had a WPW syndrome. The S loop was different from that found in atrial septal defect in 5 cases, because slurring was absent, but similar to that of atrial septal defect with severe pulmonary hypertension in 3 cases; then, QRS ≥90 msec. and preterminal slurring was C-CW in VCG_H. Complete RBBB was not found; incomplete RBBB was present in 3 cases.

Pure pulmonary stenosis (SO of RV; diastolic *underloading* of LV when severe stenosis is present): 12 cases proved by catheterization, 8 of which were confirmed during operation; age ranged from 4 to 35 years (mean age, 13 years). QRS duration was usually normal (only 2 cases ≥90 msec., and both had preterminal slurring of S loop). CW rotation always present in QRS_F

*Cases of the S_1-S_2-S_3 type with small terminal "appendage" pointing backward, upward, and to the right (2 of the 39 cases) were not considered as RBBB.

and QRS_H. The Q loop was either absent (2 cases in which the VCG started dorsally and leftward) or significantly reduced (10 cases <0.15 mv.). The R loop was always reduced (12 cases <1.0 mv.; 7 of 12 cases <0.5 mv.). The S loop was always prominent and usually neat (8 cases), similar to that found in Fallot's trilogy. When slurring was present (4 cases), it was of the preterminal type, and usually (3 of 4 cases) had C-CW rotation in the horizontal plane. The S/R quotient was notably high (11 cases >1.0 mv.; 2 of 12 cases >3.0 mv.).

Patent ductus arteriosus (DO of LV proportional to A-V shunt; SO of RV proportional to pulmonary hypertension): 81 cases confirmed either by surgery or catheterization; age ranged from 2 to 35 years (mean age, 10 years). QRS duration was usually normal (only 3 cases ≥90 msec.; mean duration, 63 msec.). C-CW rotation of QRS_F and QRS_H was the rule (67 cases), whereas CW rotation in both planes was exceptional (4 cases) and was always accompanied by severe pulmonary hypertension with or without reversed shunt. When there was C-CW rotation in both planes, 8 of 67 cases had a CW tip of R_H and signs of a large A-V shunt with significant LVO. The combination of C-CW QRS_H and figure-of-eight rotation of QRS_F was less frequent (10 of the 81 cases). Increased voltage of Q and R loops (Q >0.15 mv.; R >1.0 mv.) was frequent (69 cases); extreme voltage of both loops (Q >0.4 mv.; R >2.0 mv.) was also frequent (57 cases). The S loop was usually absent; a terminal "appendage," not slurred, was found only in 3 of the 81 cases. Signs of RBBB were always absent.

Ventricular septal defect (DO of both ventricles, proportional to A-V shunt; SO of RV usually important and proportional to pulmonary hypertension): 36 cases proved by catheterization; age ranged from 19 months to 35 years (mean age, 12 years). QRS duration was slightly prolonged (12 cases ≥90 msec.; mean duration, 78 msec.). There was C-CW rotation of QRS_F and QRS_H in 12 cases, 2 of which had a CW tip of R_H. C-CW rotation of QRS_F with CW rotation of QRS_H was found in 10 cases, 7 of which had prominent Q and S loops oriented ventrally and rightward. CW rotation of QRS_F and QRS_H was found only in 6 cases in which the mean systolic pulmonary pressure was 72 mm. Hg. Combined C-CW rotation of R_F and CW rotation of a slurred S_F, similar to that described by Toscano in cases of A-V canal, was found in 9 cases. The Q loop was usually enlarged (32 cases >0.15 mv.; 20 cases ≥0.40 mv.). The R loop was also enlarged (25 cases ≥1.0 mv.; but only 3 of the 36 cases ≥2.0 mv.; mean voltage, 1.25 mv.). A terminal "appendage" greater than 0.5 mv. was present in 24 cases, 10 of them with a definite late slurring.

Ebstein's disease (variable loading of RV; relative DO of LV when V-A shunt is present; superimposed ventricular conduction defect): 11 cases in which clinical and fluoroscopic findings were highly suggestive (enlarged RA without evidence of enlarged RV, plus poor hilar shadows and narrow base of heart); catheterization and/or phonocardiogram were also highly suggestive; age ranged from 5 to 23 years (mean age, 11 years). QRS duration was usually prolonged (10 cases ≥90 msec.; 7 of 11 cases ≥100 msec.). Frontal R loop had CW rotation in 8 cases, C-CW rotation in 2 cases, and figure-of-eight rotation in 1 case. Horizontal R loop was turned CW in 3 cases and C-CW in 6 cases; there was figure-of-eight rotation in 2 cases. Q loop was reduced (5 cases) or absent (6 cases), with some initial slurring in 9 cases (significant slurring in 4 of the 11 cases). This beginning was abnormally oriented (upward and to the left) in 8 cases. The R loop was variable (5 cases ≥1.0 mv.; mean voltage, 0.92 mv.). There was definite terminal "appendage" in 9 cases (the other 2 cases had a full-blown WPW syndrome). The terminal "appendage" was usually oriented ventrally and to the right in 7 of the 9 cases, similarly to that found in cases of RBBB. The S/R quotient was frequently high (5 of the 9 cases >0.5; 2 of the 9 cases >1.0).

2. *Acquired Heart Disease.*—

Arterial hypertension (SO of LV easily complicated with chronic coronary insufficiency): 21 cases with diastolic pressure ≥100 mm. Hg without signs of myocardial infarction; age ranged from 45 to 79 (mean age, 59 years). QRS duration was frequently prolonged (10 of 21 cases ≥90 msec.; 8 of 21 cases ≥120 msec.; mean duration, 102 msec.). When *normal intraventricular conduction* was present (11 of 21 cases), there was always a C-CW rotation of QRS_H, and most of them (9 of the 11 cases) had a C-CW rotation of QRS_F, too. The Q loop was usually absent (7 of 11 cases) or reduced (4 of 11 cases <0.17 mv.). The R loop was always dorsal and to the left, and usually downward (6 of 11 cases); it was enlarged in most of them (9 of 11 cases ≥1.0 mv.; mean voltage, 1.38 mv.). The S loop was always absent and the J point was always displaced

to the right (in all 11 cases $\geq$0.17 mv.; mean displacement, 0.35 mv.). *There were 5 cases with RBBB (4 of the 5 cases $\geq$120 msec.).* There was variable rotation of R_H but constant C-CW rotation of S_H; there was C-CW rotation of R_F and S_F in 2 of the 5 cases and CW rotation of both loops in 2 more cases. The Q loop was absent in 2 of the 5 cases and slightly reduced in the other 3 cases (mean voltage for the 5 cases was 0.08 mv.). The R loop was slightly increased (in 2 of the 5 cases >1.0 mv.; mean voltage, 1.28 mv.). The S loop was always slurred and increased (mean voltage, 0.83 mv.). *There were also 5 cases with LBBB (4 of the 5 cases $\geq$120 msec.)*, all of them with CW rotation and left posterior orientation of R_H. The Q loop was always abnormally reduced and displaced to the left (mean voltage, 0.09 mv.). The R loop was always enlarged (in all 5 cases >1.0 mv.; mean voltage, 1.86 mv.) and with slurring of its tip. The S loop was always absent, and the J point was constantly displaced (mean displacement, 1.01 mv.).

Rheumatic aortic stenosis and regurgitation (SO and DO of LV): 6 cases with basal diastolic and harsh systolic murmurs plus systolic thrill propagated to neck vessels; in most cases, the regurgitation was predominant; age ranged from 15 to 43 years (mean age, 27 years). The QRS duration was normal (only 2 cases $\geq$90 msec.; mean duration, 81 msec.). There was C-CW rotation of QRS_F and QRS_H in 5 cases, and slight CW rotation of QRS_F in 1 case. There was CW rotation of the tip of R_H in 3 cases. Q loop was usually enlarged (4 cases >0.15 mv.; mean voltage, 0.20 mv.). In only 2 cases was there a small Q loop, in one of which there was incomplete LBBB.

Mitral regurgitation (DO of LV; SO of RV if pulmonary hypertension is present): 8 cases with intense apical holosystolic murmur with axillary propagation; age ranged from 8 to 12 years (mean age, 9 years). The QRS duration was normal (8 cases <90 msec.; mean duration, 70 msec.). C-CW rotation of QRS_F and QRS_H was always present, and one case had CW rotation of the tip of R_H. The Q and R loops were constantly enlarged (Q $\geq$0.30 mv.; R $\geq$1.0 mv.), but the R loop was never greater than 2.2 mv. The S loop was always absent.

Mitral stenosis (SO of RV proportional to pulmonary hypertension; diastolic *underloading* of LV when mitral stenosis is severe): 32 cases proved during commissurotomy (mitral area <1.0 $cm.^2$ without regurgitation); age ranged from 16 to 46 years (mean age, 30 years). QRS duration was usually normal (29 cases <90 msec.; 3 of the 32 cases = 90 msec.; mean duration, 73 msec.). There was CW rotation of QRS_F in 21 cases, either with CW rotation of QRS_H (14 of the 21 cases) or with figure-of-eight rotation (7 of the 21 cases); a profile view of QRS_F with variable QRS_H was very rare (4 of the 32 cases); so was a C-CW rotation in both planes (7 of the 32 cases).* Q loop was usually absent (8 cases) or reduced (22 cases <0.15 mv.). when the Q loop was absent, there was a CW rotation of QRS_F and QRS_H. The R loop was oriented downward and to the left in 30 of 31 cases; most of them (22 of the 30 cases) were also ventral. The R loop was usually normal (0.7 mv. $\leq$22 of 32 cases $\leq$1.2 mv.) and sometimes reduced (10 of 32 cases <0.7 mv.); the mean voltage of the R loop (0.73 mv.) was slightly greater than that found in cases of mitral stenosis with tricuspid regurgitation but smaller than that in cases of atrial septal defect. S loop was frequently absent (13 of 32 cases) or small (mean voltage, 0.29 mv.) so that the S/R quotient was slightly increased (mean quotient, 0.4). Slight terminal slurring was present in 10 of the 32 cases, but the vectorcardiographic criterion of RBBB was met only questionably in one case.

Mitral stenosis and tricuspid regurgitation (SO of RV, usually severe; DO of RV proportional to tricuspid regurgitation): 6 cases with holosystolic murmur over xiphoid appendix, reinforced during inspiration (4 of which had systolic expansion of the liver, and in the other 2, mitral regurgitation could be excluded at the time of commissurotomy); age ranged from 21 to 44 years (mean age, 31 years). Duration of QRS was usually normal (4 cases <90 msec.). There was always CW rotation of QRS_F and QRS_H. The Q loop was absent in 5 cases and small (0.10 mv.) in 1 case. The R loop also was reduced (5 cases <1.0 mv.; mean voltage, 0.65 mv.). The S loop was always enlarged (in all 6 cases $\geq$0.70 mv.; 3 cases $\geq$1.0 mv.; mean voltage, 0.92 mv.), so that the S/R quotient was $\geq$1.0 in all cases. Faint slurring of the S loop was found only in 2 of the 6 cases (both with QRS $\geq$90 msec.; one was "terminal" and the other "preterminal").

Chronic cor pulmonale (SO of RV proportional to pulmonary hypertension; usually chronic coronary insufficiency in older patients): 13 cases with typical x-ray and clinical findings; age

*These 7 cases had some rightward displacement of the J point, so that they looked like cases of mild LVO, but the figure-of-eight configuration of P_H allowed a correct diagnosis of mitral stenosis.

ranged from 27 to 94 (mean age, 59 years). QRS duration was frequently prolonged (7 cases $\geq$90 msec.). There was CW rotation of QRS_F in 10 cases, in 8 of which there was C-CW rotation of QRS_H. CW rotation of QRS_H was found only in 5 of the 13 cases. The Q loop was absent in 6 cases (5 of them with the VCG starting dorsal and to the left), and reduced ($<$0.15 mv.) in 6 other cases. The R loop was almost constantly reduced (12 cases $\geq$1.0 mv.; 5 of the 13 cases $\leq$0.5 mv.). The S loop was present in 8 of 13 cases (3 of 13 cases $>$1.0 mv.), usually pointing upward, and to the right (5 of the 8 cases). The S/R quotient was $>$1.0 in 5 of the 13 cases, all of which were without Q loop and with left dorsal commencement of the VCG. Terminal slurring was found in 9 cases (only 5 of the 9 cases had a definite S loop); preterminal slurring was found in 2 of 13 cases, with C-CW rotation of tip of S_H. There was VCG evidence of RBBB in 4 of 13 cases.

Mitral stenosis and regurgitation (SO of RV proportional to pulmonary hypertension; DO of LV proportional to amount of regurgitation): 10 cases with Duroziez's rhythm and intense apical holosystolic murmur propagated to the axilla (diagnosis confirmed during commissurotomy in 3 of the 10 cases); age ranged from 11 to 50 years (mean age, 28 years). QRS duration was always normal (mean duration, 76 msec.). CW rotation of QRS_F and QRS_H (4 cases) was as frequent as C-CW rotation in both planes (4 cases). The Q loop was usually enlarged (7 cases $>$0.15 mv.; mean voltage, 0.35 mv.). The R loop was also enlarged (4 of 10 cases $\geq$1.2 mv.; mean voltage, 0.93 mv.). The S loop was always accompanied by CW rotation of QRS_F and QRS_H (mean voltage, 0.5 mv. in these 4 cases). Faint terminal slurring was found only in 1 of the 10 cases. VCG evidence of RBBB was never found.

DIAGNOSIS

Before considering the different stages of the diagnostic interpretation, we want to emphasize two of its characteristics and their underlying concepts.

The data contained in the VCG are not essentially different from the data contained in the ECG: both correspond to the electrical field of the heart as it is detected on the surface of the thorax, and both reflect the underlying cardiological conditions. This is the reason that the aim of our VCG interpretation is identical to that of the ECG interpretation,[3] i.e., we try to discover the causal relations between the electrical field of the heart, on the one hand, and the electrophysiology or the electrical abnormalities created by the clinical conditions, on the other. The systematic unfolding of these relationships is made in three stages, just as for the ECG[3]: the identification of a normal or abnormal heart; the electrophysiologic diagnosis; the clinical suggestions. Some authors limit themselves to the first and second stages, but we consider that failure to extend the interpretation to the point of clinical significance (pathologic diagnosis) makes the VCG of little use to the clinician and hinders constructive criticism by means of other diagnostic aids.

Despite these similarities between ECG and VCG, the latter registers the space-time characteristics of the heart field in a *form* which, being completely different from that of the ECG, predetermines the scope of our interpretation. For instance, in a vectorcardiographic study, we are unable to identify the rate of the heart, the mechanism of arrhythmias, or the duration of the P-R and Q-T intervals; also, we can only determine with difficulty the duration of auricular activation. On the other hand, the VCG allows an immediate and synthetic estimation of the heart field and its main instantaneous vectors; it allows a direct visualization of the phase-current relationships as well as an objective distinction between fictitious and real slurrings of the curves; most of all, it allows the ac-

curate determination of the change vectors, i.e., the orientation and magnitude of variations in the rate of voltage, through an analysis of the speed and sense of inscription of the loops.

Consequently, the situation is that of two methods which refer to the same cardiological conditions and contain the same electrical data, but these are expressed in a different form. From the point of view of methodology, we would say: the identity of their content (cardiological condition) and difference of their formal relations (graphic presentation) recommend an interpretation with the same diagnostic stages and the same diagnostic aims, but with a different technique of analysis and different integration of the elements to form a diagnostic pattern. Let us consider the three stages of diagnostic interpretation of the VCG.

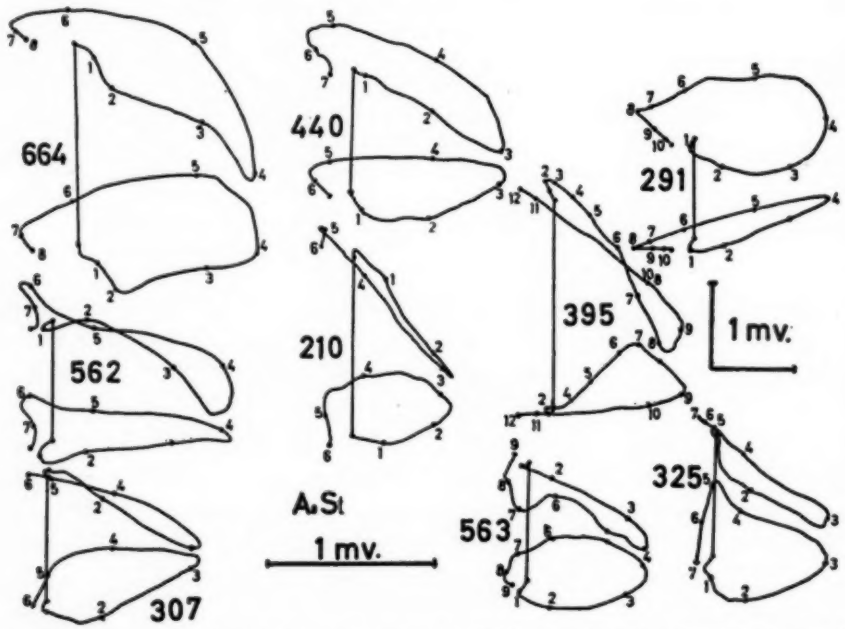

Fig. 1.—Nine cases of congenital aortic stenosis. Each case includes frontal plane (*above*) and horizontal plane (*below*). Notice the C-CW rotation in the horizontal plane in all cases (except Case 395 with complete LBBB), as well as the absence of the Q loop in Cases 664, 440, and 210 and important reduction in the other cases. Notice also the terminal "appendage" in Cases 562, 563, 291, and 325.

A. *Is the Tracing Normal or Abnormal?* Because the QRS loop is the most conspicuous part of the VCG, its analysis becomes the easiest and safest. Consequently, we always begin by examining the abnormalities of the QRS loop. Those with a greater significance for the identification of an abnormal heart refer to orientation, rotation, voltage, and trajectory of the loop, such as: an abnormal direction of the dominant vectors, i.e., a direction outside the left anteroinferior or left posteroinferior octants or, when the main vector lies in these two octants, a displacement of more than 30 degrees before or behind the frontal plane; the extreme reduction or complete absence of the Q loop, i.e., a leftward initiation of the VCG so that the start becomes indistinguishable from the centrifugal branch of the main loop; a clockwise rotation of QRS_H or a widely open

(either CW or C-CW) QRS_F; an initial slurring lasting more than 20 msec., or an intermediate slurring lasting more than 10 msec.; a late slurring outside the right posterosuperior octant; an initial or intermediate notch whose maximal deviation from the theoretical trajectory is at least one half of its length; a sudden change in the trajectory or in the speed of inscription of the QRS loop.

Besides the QRS-loop abnormalities, we look for: a CW rotation of P_F or P_H, or a figure-of-eight rotation (C-CW–CW) of P_H, especially if it is accompanied by a rightward and upward displacement of the end point of the P loop; displacements of the ventricular J point exceeding 10 per cent of the main instantaneous QRS vector; displacements of the T loop out of the left anteroinferior or left posteroinferior octants; a round T loop with uniform speed of inscription.

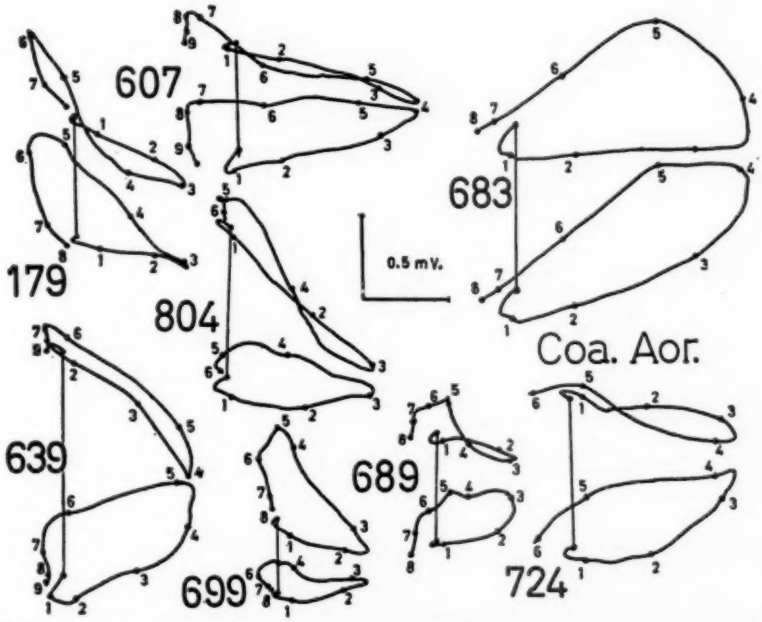

Fig. 2.—Eight cases of coarctation of the aorta. Distribution of loops similar to that of Fig. 1. Notice the C-CW rotation in the horizontal plane in all cases, and variable rotation in the frontal plane. Notice as in cases of aortic stenosis, the important reduction of the Q loop and the terminal "appendage" in Cases 179, 607, 699, and 689.

We always try to demonstrate at least three of the aforementioned abnormalities before considering the tracing to be abnormal, because some of these abnormalities can be induced by physiologic variations. For instance, a CW rotation of QRS_H can be found in normal infants,[18] in undernourished children,[18] and in the adult who lives in extremely high altitudes.[30] Some reduction of the Q loop with posterior displacement of the R loop[25] can be found in apparently normal elderly patients. The discovery of an abnormal initial slurring of the QRS loop due to a WPW syndrome is not evidence of heart disease. A rightward displacement of the J point as well as a small and round T loop can be induced by rapid heart action or the administration of digitalis. An intra-auricular conduction defect can be found in normal vagotonic subjects, and gives rise to figure-of-eight rotation of P_H.

B. *Which Is the Electrophysiologic Diagnosis That We Can Derive From the VCG?* At present, we can only integrate a few patterns with electrophysiologic significance: those of auricular enlargement, ventricular overloading, bundle branch block, A-V pre-excitation, myocardial necrosis (with or without focal block), myocardial injury, and myocardial ischemia. In this paper, we shall confine ourselves to the electrophysiologic diagnosis of ventricular overloadings, both as to the identification of the ventricle which is overloaded and the type of overloading.

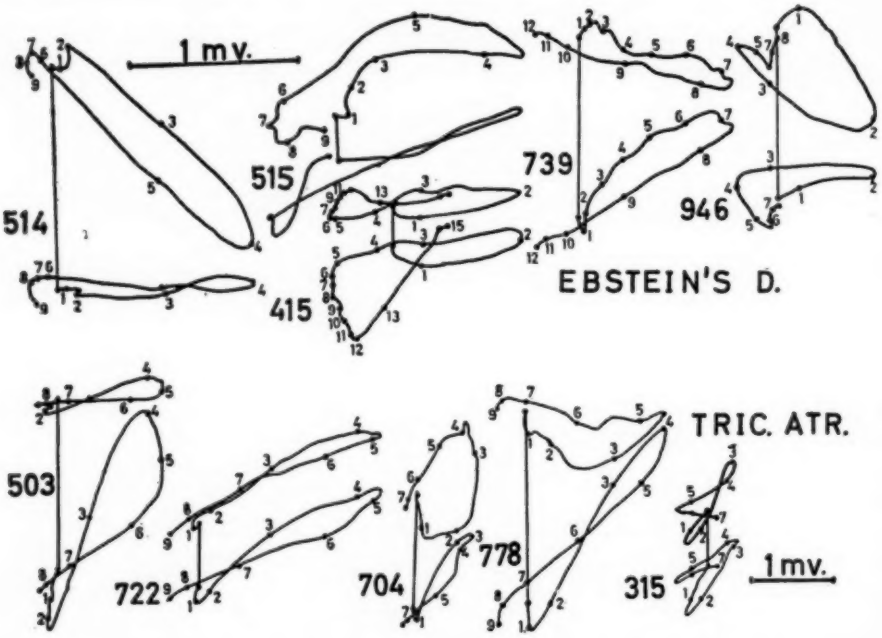

Fig. 3.—*Upper row:* **Five cases of Ebstein's disease. Notice slurring or absence of the Q loop in all cases, plus a terminal slurring. This pattern is almost exclusive of Ebstein's disease if we discard cases with myocardial infarction.** *Lower row:* **Five cases of tricuspid atresia. Notice a CW rotation of QRS_H and a large Q loop in most cases. This pattern can be observed in few cases of patent ductus arteriosus with important A-V shunt. Notice also that the two limbs of the Q loop are close together.**

1. *Right or Left Overloading Patterns.*—The essential elements for integration of these patterns are: the orientation and voltage of the dominant QRS vector, the sense of rotation of the QRS loop, the orientation and importance of the J-point displacement, the location and sense of rotation of the T loop. As always, we try to combine two or more elements, but sometimes we can hint at an overloading on the basis of a single element, provided that the VCG gives evidence of definite abnormality by the shape of other elements.

For the diagnosis of RVO, the most specific pattern is that of a widely open CW rotation of QRS_F and QRS_H, without important slurrings,[15] whereas the earliest sign is a CW rotation of QRS_F with some anterior displacement of the R loop,[9] although not necessarily accompanied by a rightward displacement of the main vectors. A marked reduction of the Q and R loops, as well as a left posterosuperior displacement of the J point and T loop, are seen rather in severe overloadings,[13,15] so that they cannot be considered as early signs. They are used

mainly to integrate a complete picture of RVO and to evaluate the *quantitative* importance of that overloading. The signs of incomplete RBBB, such as a late slurring oriented ventrally and to the right, can also be considered as early signs of RVO when observed in children or young people, provided that some ventral displacement of the centripetal branch of R and/or some CW rotation of QRS_F are present.[22]

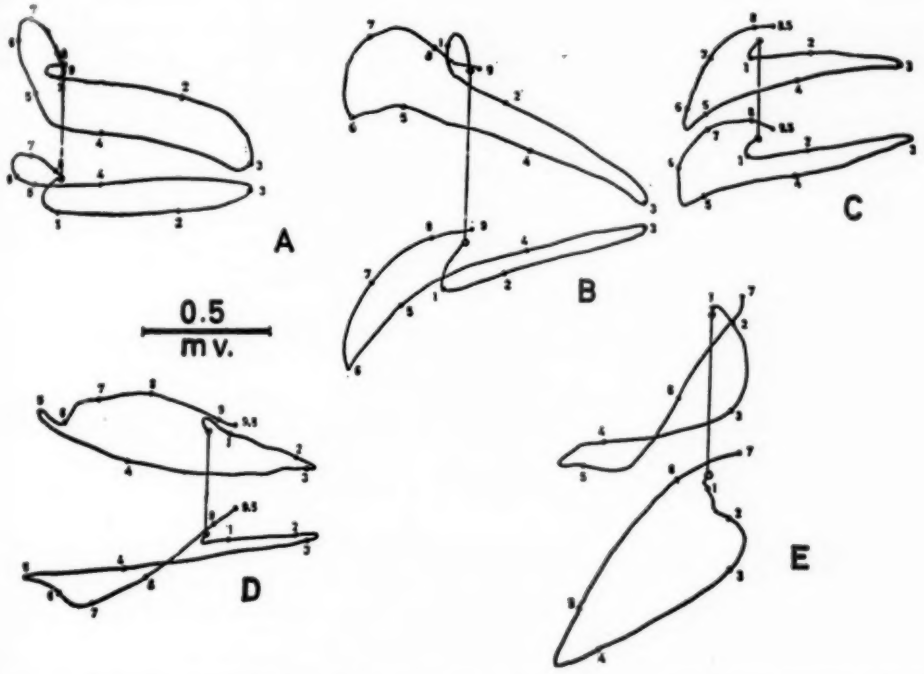

Fig. 4.—Five cases of atrial septal defect. Type *A* was usually observed with normal pulmonary pressure. Notice in this type the terminal appendage oriented to the right, and the normal voltage of the Q and R loops, indicating a normal load on the left ventricle. Type *B* was observed with mild pulmonary hypertension (systolic pressure of 35 to 40 mm. Hg). Notice the normal R loop despite the augmented voltage and slurring of the S loop. We have not observed this pattern outside of cases of atrial septal defect. Type *C* was observed with mild or moderate pulmonary hypertension (40 to 50 mm. Hg). Notice the normal R loop but CW rotation of R_H and slurring of the S loop. This pattern can also be observed in cases of mitral stenosis with pulmonary hypertension and in a few cases of mild pulmonary stenosis. Type *D* was observed in cases of severe pulmonary hypertension (≥ 70 mm. Hg). Notice the small voltage of the Q and R loops, with CW rotation of R_H as well as important slurring and C-CW rotation of S_H due to incomplete RBBB. This pattern can also be observed in cases of chronic coronary heart disease and in some cases of Fallot's trilogy. Type *E* was observed with high pulmonary hypertension (about systemic pressure values). Notice absence of Q_H, very small R loop, and widely open CW rotation of QRS_H. This pattern can also be observed in cases of "systemic" right ventricle.

For the diagnosis of LVO, the most specific pattern is that of a widely open C-CW rotation of QRS_F, with backward displacement of a neat R loop. The tip of R_H may have a CW or a C-CW rotation.[7] On the other hand, the earliest sign of LVO is a right anterior displacement of the J point, when it is accompanied by some posterior displacement of the R loop and/or a C-CW rotation of the T loop in the horizontal plane. Signs of LBBB, such as an intermediate slurring and CW rotation of the R_H, can be taken as indirect evidence of LVO, because 90 per cent of these cases show some enlargement of the LV on x-ray examination, and 60 per cent have either arterial hypertension or aortic valvular disease.[12]

A biventricular overloading pattern is less easily identified on the VCG than it is on the ECG. This overloading can be suggested when CW rotation of a neat QRS_H is accompanied by a C-CW rotation of QRS_F, by a large Q loop, by a large R loop, or by a late inscription ($\geq$ 45 msec.) of the tip of R.[11] It can also be suggested when a C-CW rotation of QRS_F and QRS_H, as obvious signs of LVO, is accompanied by a large and widely open Q loop plus some early, ventral displacement of the centrifugal branch of R.[14,31] Finally, we can make that suggestion when C-CW rotation of QRS_F and QRS_H is accompanied by a prominent, neat S loop oriented dorsally and to the right.[4]

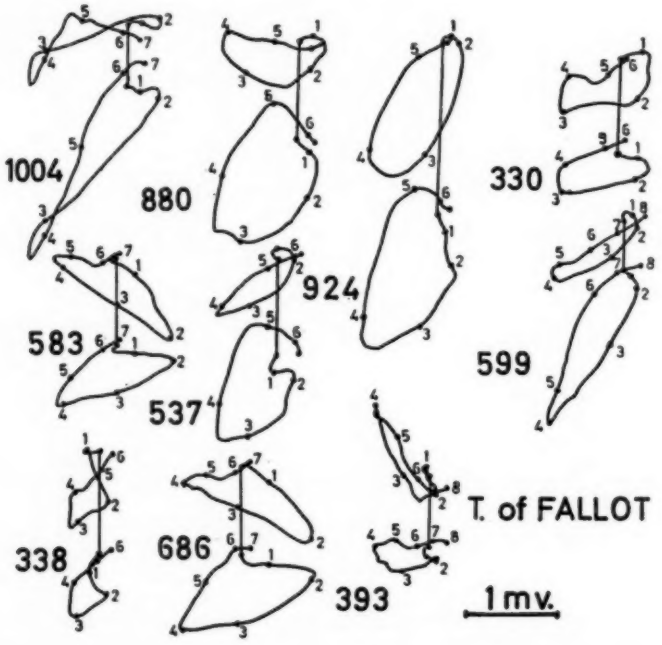

Fig. 5.—Ten cases of tetralogy of Fallot. Notice a CW rotation of QRS_F and QRS_H, important reduction of the Q and R loops, and large S loop. Notice also a widely open QRS loop in the horizontal plane, similar to the Type E of atrial septal defect.

2. *Systolic or Diastolic Overloading Patterns.*—Once we have identified the pattern of RVO or LVO, we try to differentiate whether the pattern is due to a volume or a pressure overloading. The more advanced the latter condition, the easier is the distinction on the VCG, although we cannot make the diagnosis of both volume *and* pressure overloading in one case.

If a RVO has been identified, we pay attention to the mutual relation between the S loop and the Q and R loops. Sometimes a prominent and slurred S loop, oriented anteriorly and to the right, contrasts with a Q loop which is still present and with an R_H which has normal voltage and C-CW or figure-of-eight rotation.[8] This pattern corresponds very frequently to, and permits the probable diagnosis of, a DO of RV, especially when there is CW or figure-of-eight rotation of S_H. At other times the prominent S loop, although still oriented anteriorly and to the right, is not slurred, and contrasts with a reduced or absent Q loop, and a small R loop which has forward displacement and CW rotation on

the horizontal plane.[8] In this case, a SO of RV can be diagnosed. It is interesting to note that the center of gravity of the QRS and T loops, as well as the J point, do not become importantly displaced in DO of RV, whereas in SO of RV they do. In this latter instance, the center of gravity of the QRS loop is displaced ventrally and to the right, and, consequently, the J point and the center of the T loop are displaced dorsally and to the left, because of "secondary" changes of repolarization.

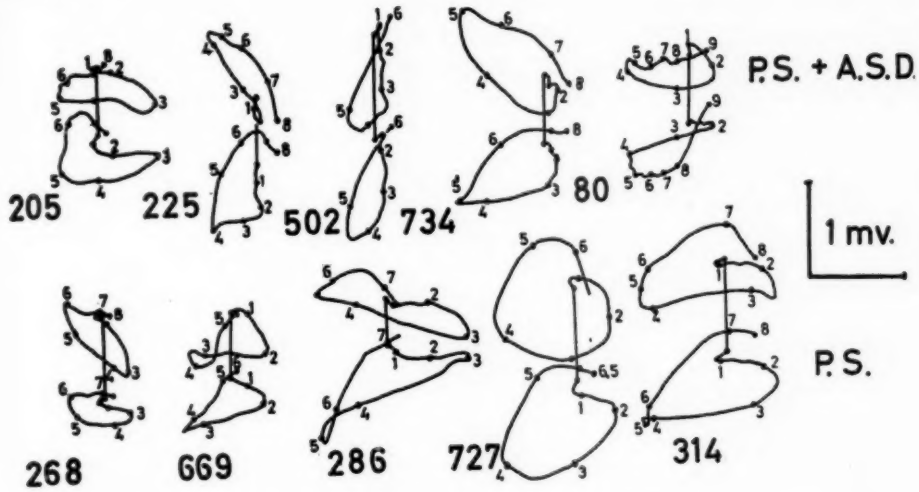

Fig. 6.—*Upper row:* Five cases of Fallot's trilogy. Notice a CW rotation of QRS_F and QRS_H, and an important reduction of Q and R loops. In Cases 502 and 80, the Q loop starts directly to the left, indicating the *extreme* overloading of the RV. In Case 80, there is also an incomplete RBBB. *Lower row:* Five cases of pure pulmonary stenosis. Notice a CW rotation of QRS_F and QRS_H, similar to that seen in the trilogy or tetralogy of Fallot. Notice also the patterns of extreme RVO in Cases 669 and 286 (this latter with incomplete RBBB).

If, on the other hand, an LVO has been identified, we pay attention to the mutual relation between the Q loop and the R loop. Sometimes the Q loop is importantly reduced or even absent, so that the VCG starts directly to the left to inscribe the centrifugal branch of the R loop.[7,8] About 90 per cent of these cases correspond to a SO of LV, usually complicated with chronic coronary insufficiency.[7] The other 10 per cent may correspond to atherosclerotic heart disease without a hemodynamic overloading, especially when an old anteroseptal myocardial infarction is responsible for the Q-loop alterations.* At other times, when the Q loop is enlarged, we make the diagnosis of diastolic overloading of the LV.† For the LV, just as we saw for the RV, the center of gravity of the QRS and T loops, as well as the J point, are not importantly displaced in diastolic overloading, whereas in systolic overloading they are.[8]

C. *What Is the Most Probable Clinical Significance of These Patterns?* At this stage of the diagnosis we do not pretend to identify the clinical entities and thus supplant the clinician. We try rather to explore the diagnostic possibilities, initi-

*Irregularities of the QRS loop, an initial slurring and a right-ventral terminal "appendage," would speak in favor of the myocardial infarction.

†A posterolateral myocardial infarction, although able itself to increase the voltage of the Q loop,[19,34] is accompanied rather by a reduced R loop plus other signs of infarction.

ating a dialogue with the cardiologist, to whom we present a partial outlook which has to be correlated with or opposed to those other partial perspectives derived from roentgenologic, phonocardiographic, hemodynamic, and clinical studies.[3] The elements used to integrate these "clinical" patterns are: (1) the ventricle which is overloaded; (2) the type of overloading; (3) the quantitative importance of the loading; (4) the concomitant intraventricular conduction defects; and (5) the aspect of the P and T loops. Besides these VCG elements, we always take into consideration the age and sex of the patient.

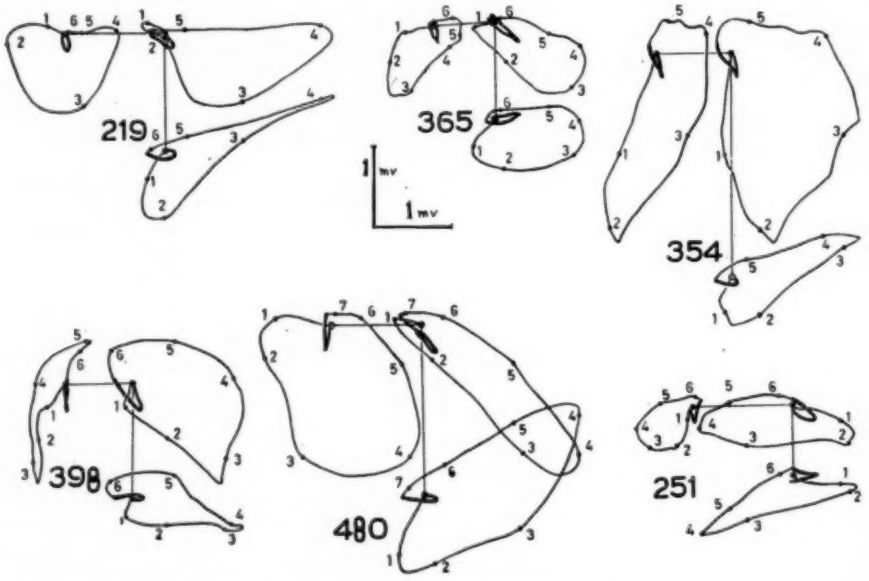

Fig. 7.—Seven cases of patent ductus arteriosus. In each case the left sagittal and frontal views are shown above, and the horizontal view is shown below. Notice a C-CW rotation of QRS_F and QRS_H, and enlarged Q and R loops in all cases, indicating DO of LV. This pattern can also be observed in some cases of severe mitral or aortic regurgitation (cf. Figs. 9 and 10).

1. *Diagnostic Orientation in RVO.*—Let us suppose that an *extreme overloading* of the right ventricle has been identified by [8,13,15,25] a widely open CW rotation of QRS and T in both planes, a complete disappearance of the Q loop, an important reduction of the R loop, and an enlarged S loop (S/R > 2), plus a posterosuperior and leftward displacement of the J point and the T loop (Fig. 5:1004; Fig. 6:734 and 286; Fig. 12:200 and 150). This pattern suggests a systolic pressure of the RV exceeding the level of the aortic pressure ("hypertrophie de barrage"[16]), so that it speaks strongly in favor of either valvular pulmonary stenosis or extreme pulmonary hypertension and leaves little room for the possibility of a noncomplicated "systemic" right ventricle.

In some other cases we can identify the pattern of *strong but not extreme overloading* of the right ventricle[8] (Donoso's type II[15]; Deglaude's type IV[13]). A widely open CW rotation of QRS in both planes is accompanied by a small Q loop in the frontal plane which is absent or scarcely seen in the horizontal plane, so that the QRS loop starts slightly anteriorly and to the left (Fig. 5:583, 537, 599, and 686). There is also a small R and a large S loop (S/R > 2), plus the usual

"secondary" changes of the J point and the T loop. This pattern indicates an intraventricular pressure of the RV which approximately equals the level of the aortic pressure ("hypertrophie d'adaptation"[16]), so that, although not being exclusively diagnostic of a "systemic" RV, it suggests with high probability this condition (Fallot's tetralogy, transposition of great vessels, patent ductus arteriosus with V-A shunt, etc.)

The patterns of *mild or moderate RVO* usually correspond to pulmonary hypertension accompanying mitral stenosis or atrial septal defect and, less frequently, pulmonary stenosis or primary pulmonary hypertension. Such patterns (Fig. 4, *A* and *C*; Fig 6:268; Fig 11:256 and lower row) can be identified by the normal voltage of the Q and R loops with some CW rotation of QRS_F,

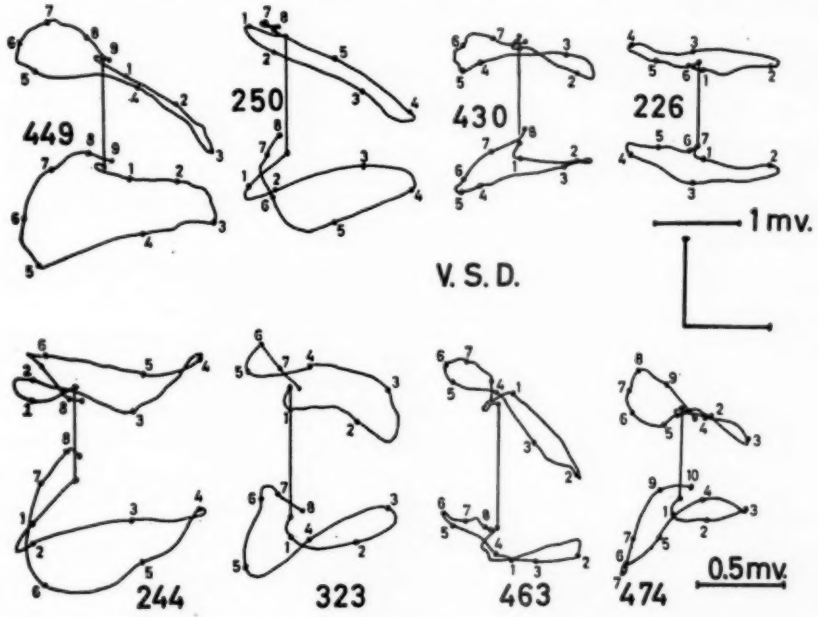

Fig. 8.—Eight cases of ventricular septal defect. Notice the signs of biventricular overloading: CW rotation of QRS_H and C-CW rotation of QRS_F, with or without large Q and R loops. A similar pattern could be observed in cases of severe mitral regurgitation with important pulmonary hypertension.

whereas R_H has a CW or figure-of-eight rotation or only an anterior displacement with slight C-CW rotation.[8] Once we have identified one of these patterns, we pay attention to the P loop and the slurring of the S loop. The so-called "mitral" P loop (bimodal P_F associated with CW rotation and posterior displacement of the tip of P_H), indicates mitral stenosis, especially if some anterior displacement of the R loop is present (Deglaude's type I and II[13]). A normal or slightly modified P loop, contrasting with an obvious *terminal* slurring of the S loop, bespeaks atrial septal defect, especially if the S loop is prominent and shows a CW rotation in the horizontal plane and some downward displacement in the frontal plane[22] (Fig. 4, *B* and *C*). We must mention that normal infants as well as undernourished children may show the patterns of mild or moderate RV preponderance,[18] so that these patterns can easily be misinterpreted as indicating mitral stenosis or an atrial septal defect; however, the normal aspect of the P loop, the lack of im-

portant terminal slurring, and the age of the patient can prevent misinterpretation. On the other hand, an advanced degree of incomplete RBBB (preterminal slurring and C-CW rotation of S_H) with mild RVO can be confused with the RBBB of atherosclerotic heart disease[7]; but the CW rotation of the frontal QRS loop and some downward displacement of the tip of the S loop incline the diagnosis in favor of atrial septal defect, especially if these features are found in a young adult.[22]

A peculiar situation is found when the VCG shows signs of mild or moderate RVO with a terminal slurring suggestive of incomplete RBBB, but the Q loop is not clearly seen, and the initiation is abnormally slurred and oriented upward and to the left. When this pattern is found in older patients, the most likely possibility would be a myocardial infarction either with RBBB or intrainfarction block. However, when found in children or young patients, it suggests the association of RBBB and WPW syndrome,[6] pointing, in our experience, to Ebstein's disease, and, less frequently, to a normal heart or noncomplicated atrial septal defect (Fig. 3:514, 515,946).

2. *Diagnostic Orientation in LVO.—Extreme overloading of the LV* can be identified by a widely open C-CW rotation of QRS_F with a large R loop oriented backwardly and leftward; the tip of this loop or an important portion of its "body" shows a CW rotation in the horizontal plane, without much intermediate slurring[4,7] (Fig. 3:503, 722, 704 and 778; Fig. 9:187; Fig. 14:269). This pattern of extreme LVO is frequently accompanied, in the frontal view, by a bifid appearance of the tip of the R loop.[11,31] Consequently, QRS_F has a triangular shape, wherein the more prominent the second (upper) peak the more severe is the overloading of the LV, and the more delayed is the inscription of the intrinsicoid deflection of the leads oriented to the left (Fig. 9:478 and 446; Fig. 10:46). The vectorcardiographic signs of extreme LVO usually correspond to severe valvular aortic lesions, advanced arterial hypertension, or patent ductus arteriosus with high A-V shunt. They can also be seen in cases of moderate LVO, as in tricuspid atresia,[17,36] because of the *hypotrophy* of the RV. If the signs of extreme LVO coincide with a reduced or absent Q loop, arterial hypertension, syphilitic aortic insufficiency, and predominant aortic stenosis are the most likely possibilities. In contrast, if the Q loop is very prominent, predominant aortic insufficiency, a large ductus arteriosus, and severe mitral regurgitation, i.e., a large DO of LV have the highest probabilities. In the peculiar case of a large Q loop which has its two limbs close together or superimposed,* associated with an R loop showing a CW rotation in the horizontal plane and an upward displacement in the frontal plane, the odds favor a tricuspid atresia, provided that the R loop has no conspicuous slurring.

Moderate or mild overloading of the LV is identified by the presence of a C-CW rotation of QRS_F and QRS_H, and a posterior displacement of the QRS loop, as in extreme LVO. Nevertheless, the tip of R_H has no CW rotation, and QRS_F is not necessarily bifid, or, if it is, the first peak is more prominent than the second (Fig. 1:664, 440, 291, 325; Fig. 2:639, 699; Fig. 7:480). The diagnosis is suggested,

*We feel that it is the superimposition of the two limbs which reflects the *hypotrophy* of the RV, whereas a widely open C-CW rotation of the Q_H loop would reflect a concomitant *hypertrophy* of the RV.

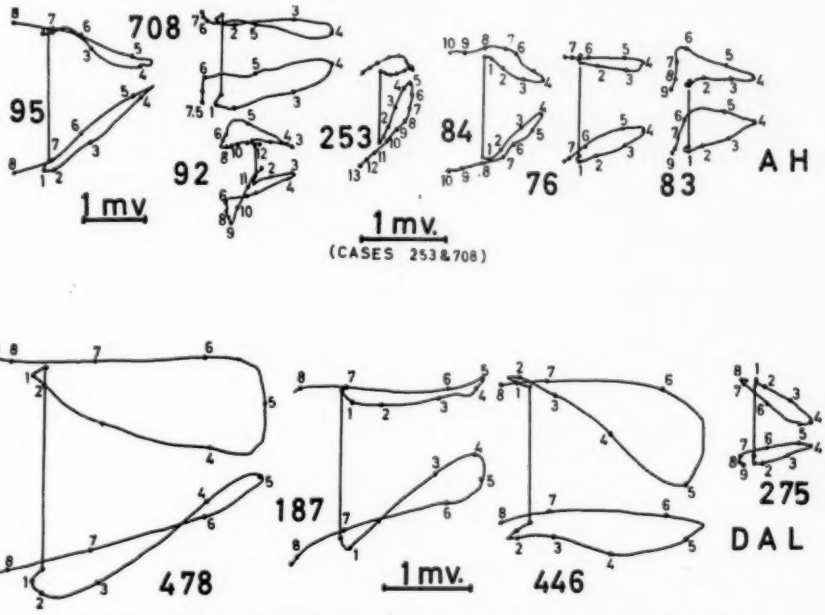

Fig. 9.—*Upper row:* Seven cases of arterial hypertension. Notice a reduction of the Q loop in all cases, and a C-CW rotation of QRS_H when normal intraventricular conduction is present. CW rotation of QRS_H in Cases 253 and 84 is due to LBBB, whereas Case 92 had a RBBB. The pattern shown in Cases 95, 708, 76, and 83 can also be observed in instances of congenital aortic stenosis or coarctation of the aorta. *Lower row:* Four cases of double aortic lesion. Notice the large Q and R loops, as well as a CW rotation of the tip of R_H in Cases 478 and 187, indicating extreme LVO. This pattern can also be found in cases of severe mitral regurgitation or tricuspid atresia.

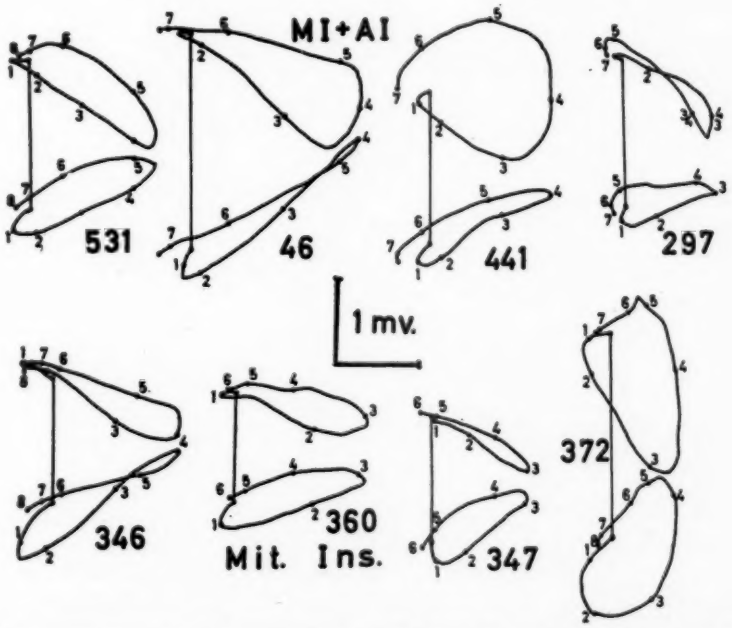

Fig. 10.—*Lower row:* Four cases of pure mitral insufficiency. Notice a C-CW rotation in both planes, as well as large Q and R loops. These loops could be observed in some cases of patent ductus arteriosus or double aortic lesion (especially in Case 346 with a CW rotation of the tip of the R_H loop). *Upper row:* Cases shown here correspond to mitral and aortic regurgitation and are not discussed in the text because they present a morphology almost identical to that seen in cases of isolated pure mitral insufficiency or aortic insufficiency.

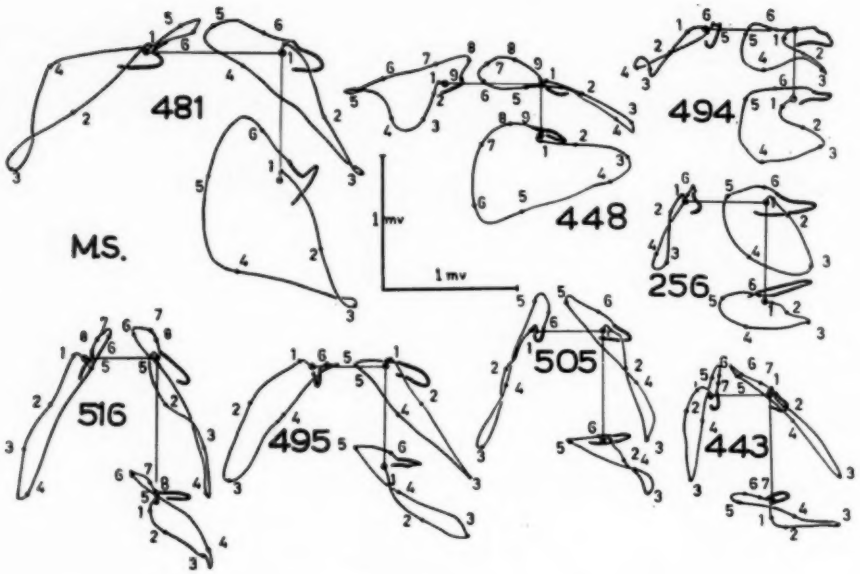

Fig. 11.—Eight cases of pure mitral stenosis. Distribution of loops similar to that of Fig. 7. *Upper row:* Four cases with signs of important overloading of the RV, such as CW rotation of QRS_H, and small voltage of the Q and R loops. Compare these loops with those of Figs. 5, 6, and 12. *Lower row:* Four cases with signs of moderate RVO, such as anterior displacement of the R loop and C-CW rotation of R_H.

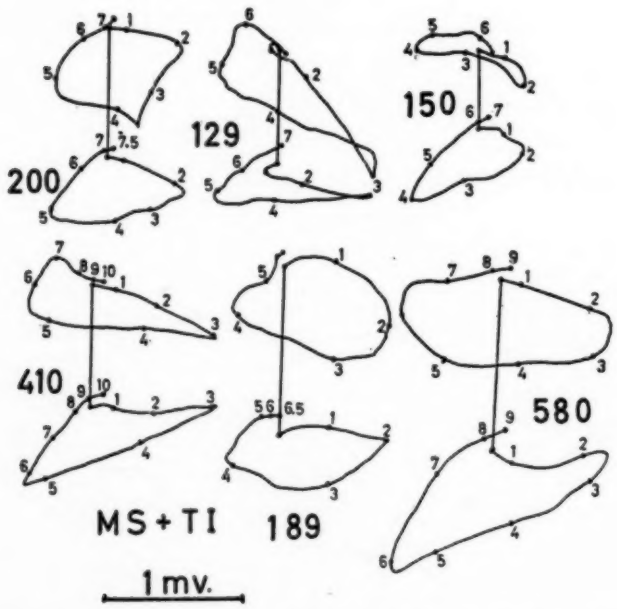

Fig. 12.—Six cases of mitral stenosis and tricuspid insufficiency. Notice a CW rotation of QRS in both planes, as well as a prominent S loop. Notice also the absence of the Q loop in all cases except Case 129. This pattern corresponds to extreme overloading of the right ventricle. Compare these cases with those of Figs. 6 and 11.

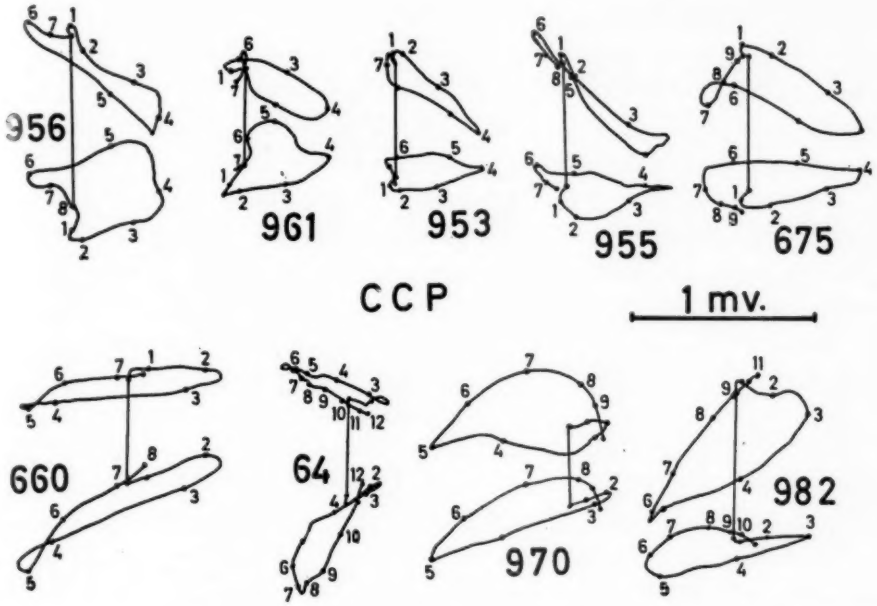

Fig. 13.—Nine cases of chronic cor pulmonale. *Upper row:* Cases with few signs of RVO (C-CW rotation of QRS_H and CW rotation of QRS_F). *Lower row:* Cases with signs of extreme right ventricular overloading (CW rotation of QRS_H, absence of Q loop, and prominent S loop).

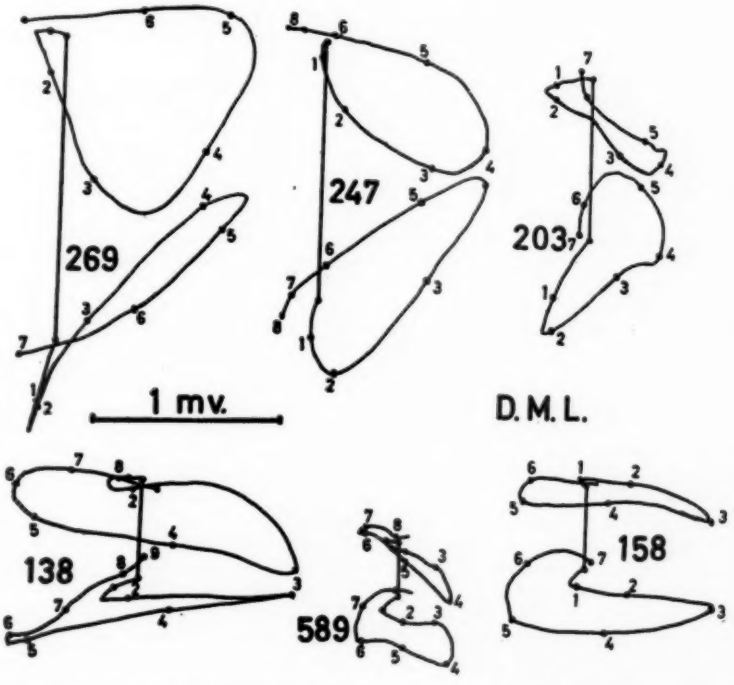

Fig. 14.—Six cases of double mitral lesion. *Upper row:* Cases with predominant regurgitation. Notice the C-CW rotation of QRS_F and the large Q and R loops, especially in Case 269, which shows CW rotation of QRS_H. *Lower row:* Cases with predominant stenosis. Notice a CW rotation in both planes (indicating RVO) but large Q and R loops (indicating LVO).

as in the previous group, by the analysis of the Q loop. However, the probabilities of tricuspid atresia are extremely few. On the other hand, if the Q loop is prominent, the descending order of probable diagnosis would be: patent ductus arteriosus, ventricular septal defect, and double aortic lesion.

3. *Diagnostic Orientation in Biventricular Overloading.*—Each one of the patterns of biventricular overloading mentioned under the heading of right or left overloading constitutes the basis for the clinical suggestions. Thus, a large Q and/or a large R loop with CW rotation of QRS_H and C-CW rotation of QRS_F suggest* a ventricular septal defect[11] or an important mitral regurgitation with severe pulmonary hypertension[4] (Fig. 8:250, 226, 244). A C-CW rotation of QRS_F and QRS_H, associated with a widely open Q_H and some anterior bowing of the centrifugal branch of the R loop, would suggest a patent ductus arteriosus[11,14] (less frequently a ventricular septal defect or a mitral regurgitation) with pulmonary hypertension (Fig. 7:480, 265; Fig. 10:346, 372; Fig. 14:247). Finally, a C-CW rotation of QRS_H with a prominent S loop backwardly oriented bespeaks arterial hypertension with chronic cor pulmonale, especially if it is found in older patients (Fig. 13:956, 961).

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*The QRS pattern described by Toscano[32] as suggestive of A-V canal correlates with this description in regard to the peculiarity of having a slurred CW rotation of S_F. This pattern is easily confused with that of ventricular septal defect complicated by a high degree of incomplete RBBB.

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Annotations

Central Nervous Control of the Renal Circulation

It is no longer possible to approach the topic of nervous control of the circulation in terms of simple reflexogenic mechanisms. Although several types of cardiovascular receptors have been described, the precise role of these receptors in normal physiology is not completely understood. In addition to afferent pathways from these receptors, the central nervous system has been shown to have pathways that could permit very complex integration of events requiring adjustments of the cardiovascular system. Indeed, the autonomic nervous system is represented at every level of the central nervous system from the spinal cord to the cerebral cortex.[1] In view of the apparent wide distribution of autonomic representations, one must approach the study of the central nervous control of the circulation from the viewpoint of determining the functional significance of the various nervous structures that can affect the circulation.

A further problem exists in evaluating the results of experiments designed to demonstrate any facet of cardiovascular control. The results of such experiments have to be considered in terms of the over-all physiologic responses to the experiment. The circulation to any given region may be affected not only by mechanisms acting directly on that region, but also by adjustments occurring in remote circulatory beds. This point is of the greatest importance if our understanding of the relationships between living habits and the incidence and course of cardiovascular disease is to be furthered.

As an example of these problems of interpreting physiologic data obtained in experiments designed to study the function of a part of the circulation the data given in Table I may be considered. These data are the clearance values of para-aminohippuric acid obtained in a series of five experiments conducted on the same subject. For practical purposes, these clearances are a measure of the renal plasma flow of the subject.

TABLE I. RENAL PLASMA FLOW DATA (PAH CLEARANCES) FROM 5 DIFFERENT EXPERIMENTS CONDUCTED ON 1 SUBJECT

EXPERIMENT NUMBER	CONTROL PERIOD (ML./MIN.)	EXPERIMENTAL PERIOD (ML./MIN.)	POSTCONTROL PERIOD (ML./MIN.)
1. (happy)	742	538	682
2. (fearful)	795	652	649
3. (depressed)	795	400	606
4. (cold)	692	518	639
5. (exercise)	744	442	—

Experiments 1, 2, and 3 of Table I involved the induction of an emotional state in the subject. This was done by having the hypnotized subject listen to a prerecorded dramatization during the experimental period. Experiment 1 was intended to produce a feeling of happiness and well being. Experiment 2 was designed to produce fear, and Experiment 3 was designed to produce

depression. The clearance periods were each 20 minutes long in the first three experiments. The subject was recumbent, relaxed, and awake in the first control period. He was hypnotized and listened to the recorded dramatization in the experimental period. The stories lasted the full 20 minutes of the clearance period. The subject was awake and relaxed in the postexperimental control period.

The story technique has been found to be very effective in altering the emotional state of the subject, as judged by methods described elsewhere.[4]

The pulse rate and blood pressure of the subject showed little alteration during the course of these experiments. The depression story produced the lowest PAH clearance value seen in these experiments.

Experiment 4 followed the same format of the first three experiments. In the experimental period, the subject was hypnotized and his left hand was placed in an ice-water bath. He was given suggestions of extreme pain and discomfort. The control blood pressure was 125/70 mm. Hg. His pressure averaged above 150/110 mm. Hg throughout the experimental period. The renal plasma flow showed a significant drop during the experimental period.

Experiment 5 was an exercise experiment and did not involve the use of hypnosis. The control and experimental periods were each 1 hour long. The exercise consisted of walking on a treadmill set at a 5 per cent grade and a speed of 3 miles per hour. This amount of exercise resulted in a two and one-half-fold increase in the resting pulse rate and a six and one-half-fold increase in the metabolic rate. The exercise level used here represents a severe task for the average medical student.

These experiments illustrate the fact that changes in the blood flow through a given region or organ can be altered in the same direction by quite different mechanisms. The first three experiments involved essentially pure emotional stimuli. The changes seen in the renal plasma flow were brought about through associations that began at the level of the cerebral cortex. The responses to the story material may even involve complex integrations with the basic emotional and personality characteristics of the subject.

The fourth experiment produced a marked, general vasoconstriction in response to a particularly painful experiment. Peripheral receptors and their associated pathways were involved. The subjective sensations were reinforced by the hypnotic suggestions. This resulted in a marked pressor response on the part of the subject, a response in which the renal circulation participated.

The exercise experiment served as a reference that is readily appreciated by physiologists. The reduction in renal plasma flow here may have resulted in large measure from effective shunting of the cardiac output through the active muscle tissue and through the cutaneous vessels. The physiologic problems posed here involved not only those associated with the muscular work but also those associated with temperature regulation, since exercise of the severity used will produce a rise of two to three degrees Farenheit in the body temperature.

The series of experiments presented here show that the renal circulation can be altered by several very different mechanisms. It is apparent that high central representations of the autonomic nervous system can be activated and cause marked changes in the renal circulation. Also, circulatory adjustments taking place in other tissues may have a marked influence on renal blood flow. The exact evaluation of the data obtained involves a complete understanding of the over-all response of the cardiovascular system to the various experimental procedures used. A fairly complete analysis of this sort is necessary if a clear understanding of the role of the renal circulatory bed in these experiments is to be appreciated. It is only by such complete information about the cardiovascular system that we can gain a clear understanding of the manner in which this system will react to the everyday stresses of an individual.

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Uremia, the ECG, and Levels of Serum Potassium

Uremia, according to Skouby,[1] will produce some unexpected alterations in the electrocardiogram. We have come to associate the prominent U wave, or as Skouby prefers, "the positive after-potential," with hypopotassemia, not with hyperpotassemia. But, according to Skouby, when acute uremia supervenes, the positive after-potential occurs in the presence of an associated hyperkalemia. The phenomenon appears to be confined to patients suffering from acute renal failure. Some 24 of 37 such patients exhibited this finding. In chronic renal failure it was seen in but 6 of 122 consecutive cases; and of the six the U wave could be explained by some mechanism other than chronic uremia in five.

Thus, according to these observations the presence of prominent U waves in an uremic subject with normal or elevated serum potassium points to the diagnosis of acute failure of erstwhile normal kidneys and away from the diagnosis of ultimate deterioration in long-enfeebled organs. The implication of this observation is such that, should it meet with confirmation, at hand could be a ready solution to the sometime diagnostic dilemma of: "Are we really dealing with an acute renal shutdown?"

Another effect of uremia on the ECG is one that might be called a "quenching effect." The familiar changes characteristic of hyperkalemia according to Skouby[2] appear in uremia only at higher than usual levels of serum potassium or, in some instances, not at all.

The generalization that could be drawn from these two observations, if they meet with confirmation, is that uremia opposes the effects of potassium on the ECG and promotes a "hypokalemic type" of ECG, whatever (up to a point) the level of serum potassium. Explanation of the observed effects of uremia on the ECG must wait at least the day when the interior, as well as the exterior, of the cardiac cell has had quantitative chemical dissection, and the time of more complete understanding of the chemistry of acute and chronic uremia.

Skouby's observations behoove one to re-examine case records of patients with acute and chronic renal failure in order to determine whether overlooked in them are facts that agree with his observations.

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The Surgical Treatment of Aortic Stenosis

At the present time there are several surgical techniques for the treatment of aortic stenosis.[1,2] One of these methods consists of passing a finger into a pouch which has been sewed onto the aorta, in an attempt to dilate the stenotic valve. Another blind technique consists of passing a dilator through a stab wound in the left ventricle and into the aortic valvular area. Although these methods have been recommended by pioneers in heart surgery and people who have performed a large number of commissurotomies, it would seem that at this time the advantages of open-heart surgery for the treatment of aortic stenosis should be presented.

In patients having congenital aortic stenosis with a fibrous stenosis, not nearly so satisfactory a split can be obtained by a blind technique as by a technique which permits direct vision. With the open-heart technique the stenotic commissure can be cut in the right place, with little, if any, danger of producing aortic insufficiency. The patient will obtain a very satisfactory relief of the aortic stenosis. When the blind technique is used, a satisfactory split is frequently not obtained, and instead of splitting the fibrous commissure the valve cusp may be split, thereby producing a very severe aortic insufficiency. There is very little danger of producing aortic insufficiency in patients with aortic stenosis of the congenital type when the direct technique is used and the stenotic valve is visualized.

In congenital aortic stenosis instead of the usual valvular stenosis there may be subaortic stenosis. It is difficult, sometimes impossible, with the blind technique to perform a satisfactory resection in these patients. With open-heart surgery, however, the subaortic stenosis can be resected under direct vision.

In the patient with aortic stenosis caused by rheumatic heart disease, the stenosis may be fibrous or the valve may be heaped with calcium. In the patient with the fibrous stenosis, again under direct vision an extremely satisfactory commissurotomy can be performed and the patient can be restored to a perfectly normal existence. When a blind technique is used, aortic insufficiency may be produced or the stenosis may not be relieved.

In the patient with moderate or severe calcification of the aortic valve, the closed techniques are useless, for the cusps are immobile because of the large piles of calcium, and cracking of the commissure, even if feasible, is of no avail. Even after a commissurotomy is performed, the cusps are so calcified that they cannot move and the calcium is so massive that it obturates the aortic lumen. For this reason it is necessary to use direct-vision surgery and remove the calcium from the cusps and restore them to a normal or almost normal function. This is now a feasible and practical method of treating severe calcific aortic stenosis.

The mortality rate in the treatment of patients with aortic stenosis by the open-heart technique should be no higher than 10 to 20 per cent and will depend not so much on the type of the stenosis as on the severity of the cardiac damage and the illness of the patient at the time of operation. On the other hand, the mortality rate in the same group of patients treated by closed techniques will not only be much higher but the number of patients cured or improved will be far fewer and the production of aortic insufficiency far greater.

It would appear that open-heart surgery has many advantages over pre-existing techniques for the treatment of aortic stenosis.

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Cholinergic Vasodilator Nerves to Human Skeletal Muscle

In man, cholinergic vasodilator fibers to vessels in the skin of the forearm are activated during heating of the body.[1] Until recently the only evidence for the existence of similar fibers to vessels in skeletal muscle came from the experiments of Barcroft and Edholm[2] on posthemorrhagic fainting; it was not known whether these fibers were used under more normal conditions of life. There is abundant evidence for the existence of cholinergic vasodilator fibers to skeletal muscle in animals.[3-5] It has been shown by Abrahams and Hilton[6] that stimulation by electrodes implanted into places in the brain which discharge these fibers in the anesthetized cat also provoke the "flight or fight" reaction in conscious cats. This suggested that the emotional stress associated with flight or fight may discharge the vasodilator fibers to skeletal muscle. It is known that emo-

tional stress in man can cause an increase in blood flow in the forearm, and although it has been claimed by Wilkins and Eichna[7] that this response is partially mediated through sympathetic nerves, it has generally been attributed to release of adrenaline.[8] Blair and collaborators[9] have recently obtained evidence that the response is largely mediated by cholinergic vasodilator fibers to blood vessels in muscle.

Periods of emotional stress lasting 2 to 3 minutes were produced in male medical students by frightening them as much as possible. The subject was led to believe that he was bleeding profusely and that the operators were worried. Many of the subjects became alarmed, and the blood flow in the forearm, as measured by the plethysmograph, increased to as much as 50 ml./100 ml./min., but there was little or no change in the blood flow in the hand. Since there was no corresponding increase in arterial pressure, the increase in flow in the forearm was due to vasodilatation in the forearm. In similar experiments there was a marked rise in the oxygen saturation of blood sampled from deep veins predominantly draining muscle,[10] paralleling the increase in blood flow simultaneously recorded with a plethysmograph in the opposite forearm. However, there was no change in the oxygen saturation of blood sampled from superficial veins predominantly draining the skin of the forearm. In these experiments, therefore, the vasodilatation was confined to blood vessels in muscle. The response was found to be reduced and occasionally abolished in forearms in which the median, radial, and ulnar nerves had been blocked above the elbow with local anesthetic solution,[11] but was not depressed in forearms in which only the cutaneous nerves were blocked.[12] In 5 patients with a unilateral sympathectomy, mental arithmetic[8,13-17] was used as the stressing stimulus; this produced an increase in blood flow through the normal forearm, but little or no change in the sympathectomized forearm. The response is, therefore, largely mediated through sympathetic nerves. Since atropinization of one forearm by the intra-arterial infusion of 0.3 mg. of atropine[1] also greatly reduced or abolished the vasodilatation, it was concluded that cholinergic vasodilator nerves contribute to the response. In other experiments, Blair and co-workers[18] have shown that the response is unaffected by the intra-arterial infusion of a sympatholytic drug, bretylium tosylate, in a dose which effectively blocks such well-known vasoconstrictor reflexes as the response to the Valsalva maneuver (which occurs in vessels in muscle) and to general cooling of the body (which occurs in vessels in skin). This provides further evidence that the sympathetic fibers mediating the response are not adrenergic.

It is difficult to say whether or not vasodilator nerves to vessels of the skin participate, but since an increase in blood flow in the skin was not observed in any of the experiments in which it was sought, it seems unlikely that it occurred in each of the experiments in which atropine was used. The experiments also provide evidence of vasodilator activity at low levels of flow, and, therefore, presumably in the presence of vasoconstrictor tone. This is in keeping with the results of experiments on animals that suggest that the vasomotor centers which control vasoconstrictor and vasodilator fibers to muscle are anatomically and physiologically distinct.[19-21] Blair and associates[9] suggest that the cholinergic vasodilator fibers to skeletal muscle are activated by the emotional experiences of everyday life.

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Subendocardial Myocardial Infarction

The criteria for the clinical diagnosis of subendocardial myocardial infarction remain confusing and obscure, despite a considerable volume of literature on the subject. One of the most important sources for the establishment of such criteria, namely, clinicopathologic correlations, tends to be meager because of the low mortality rate of persons with this condition. In our series at the Long Island College Hospital there has been a mortality rate of 28.6 per cent for all types of myocardial infarction in the years 1955 through 1958 (1,058 cases with 303 deaths), whereas there has been a mortality rate of only 5.9 per cent for subendocardial infarction during the same period (171 cases with 10 deaths).

A further basic source of confusion lies in the lack of a uniform definition of the thickness of the subendocardial layer of the myocardium. Unfortunately, it has no anatomic boundary. Thus, investigators have set their own limits on its extent. Some have designated only lesions of the inner third of the myocardium as subendocardial lesions, whereas others have included lesions of the inner half, or more, of the myocardium as subendocardial infarcts. This variation in definition of the thickness of the subendocardial layer has led to variation in the electrocardiographic patterns ascribed to this lesion. Those investigators who have reported infarcts limited to the inner third of the myocardium have described only RS-T segment depression and T-wave inversion, except in Lead aV_R, with these lesions, whereas those who have included a greater thickness of infarcted myocardium have described lowered R waves or deep Q waves as well as RS-T segment and T-wave changes. If the findings of Prinzmetal and collaborators[1] are reviewed, one finds that the inner third of the myocardium can be damaged without the production of abnormal Q waves and with only insignificant lowering of R waves. It becomes evident, then, that there is no fundamental discrepancy in electrocardiographic concept, but only in the definition of the thickness of the subendocardial layer of the myocardium.

Since there is no anatomic boundary to the subendocardial layer, it would seem suitable to use the electrical limitations of the QRS complex as a boundary for this layer. Therefore, one could define the subendocardial layer as that layer of the myocardium which, when damaged, will not produce any significant abnormality in the QRS complex of the electrocardiogram. Anatomically, then, the subendocardial layer would be limited to the inner third of the myocardium.

This restriction of the definition of the subendocardial layer to the inner third of the myocardium and, therefore, the area which is reflected only by changes in the RS-T segment and T waves, makes the electrocardiographic diagnosis of subendocardial infarction more difficult, for these changes may simulate changes which result from such functional states as increased vagal activity or hyperventilation. A proper differentiation may be made, however, if one will follow rigidly two rules: (1) The RS-T segment depression, present in the leads approximating the infarction, must be accompanied by RS-T segment elevation in Lead aV_R. (2) The deeply inverted T waves, which are also present in leads approximating the lesion, must develop progressively and disappear gradually in not less than several days, and usually in several weeks or months. The inverted T waves of functional states are fleeting and do not show such steady progression.

Although the majority of subendocardial infarctions take place spontaneously in a manner similar to other myocardial infarctions, there is a significant group which results from generalized myocardial anoxia. The subendocardial layer of the myocardium, with its distal position in relation to the epicardial origin of the coronary arteries and its proximal position to the high-pressure chamber of the left ventricle, is the layer of the myocardium most vulnerable to the effects of anoxia. Therefore, subendocardial ischemia sufficient to produce subendocardial infarction may develop, without far advanced coronary atherosclerosis, in such situations as pulmonary edema, postoperative shock, and shock associated with severe gastrointestinal bleeding. If advanced age, and, thus, increased coronary atherosclerosis are added to such a stress reaction, a subendocardial infarction is the more likely to develop. The physician who has serial electrocardiograms recorded under such circumstances will occasionally uncover unsuspected subendocardial myocardial damage.

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Book Review

PÄDIATRISCHER EKG ATLAS. By Priv.-Doz. Dr. Wilhelm Heck, Oberarzt der Univ.-Kinderklinik Göttingen, and Dr. Joachim Stoermer, Wissenschaftl. Assistent der Univ.-Kinderklinik Göttingen. With a foreword by Prof. Dr. Gerhard Joppich, Direktor der Univ.-Kinderklinik. Stuttgart, 1959, Georg Thieme Verlag, 230 pages, 161 illustrations. Price DM 78. (U.S. and Canada: Intercontinental Medical Book Corporation, New York 16, New York.)

As the title implies, this book is almost entirely an atlas of electrocardiographic changes in childhood. The atlas is preceded by a 29-page introduction dealing with technique, statistical standards for normal in the various pediatric age groups, and electrocardiographic positions and rotation of the heart.

The main section consists of 161 illustrations of actual tracings, usually including 12 leads. All the commonly encountered congenital and acquired lesions are presented. Each tracing is accompanied by a legend which gives very brief clinical data and the electrocardiographic interpretation. Both the printing and the paper are of high quality. The tracings show uniform technique, are easily read, and usually include two complexes for each lead. Time markings are present in all tracings but are not as readily discernible as one might wish.

The book would probably be most useful as a reference for German-reading cardiologists whose experience with children is limited, and who need an occasional reminder of the range of patterns seen in the common cardiac lesions of childhood.

Announcements

THE UNIVERSITY OF TEXAS POSTGRADUATE SCHOOL OF MEDICINE is pleased to announce a comprehensive SYMPOSIUM ON CORONARY ARTERY DISEASE, scheduled for Nov. 28 through Dec. 2, 1960. The symposium will be held in the Texas Medical Center, Houston, Tex., and the program will be presented by six outstanding guest lecturers augmented by a local faculty. As in previous programs, extensive use will be made of the clinical facilities of a number of local participating institutions.

This five-day program has been approved by the Academy of General Practice for Category I Credit. No tuition will be charged; however, for those physicians desiring AAGP credit a $5.00 registration fee will be charged.

For further information write: Office of the Dean, The University of Texas Postgraduate School of Medicine, 410 Jesse Jones Library Building, Texas Medical Center, Houston 25, Tex.

THE SOCIETY FOR BALLISTOCARDIOGRAPHIC RESEARCH was founded on April 14, 1960. Applications for membership should be directed to the Secretary, Abraham Noordergraaf, Ph.D., Department of Medical Physics, Physics Laboratory, Bylhouwerstraat 6, Utrecht, Netherlands. Dr. Noordergraaf will also accept orders for the Proceedings of the first congress, which was held in April, 1960, and presided over by Professor H. C. Burger.

Persons living in North and South America may apply for membership and obtain information by writing to the Secretary of the BALLISTOCARDIOGRAPH RESEARCH SOCIETY, DeWitt H. Smith, M.D., New Jersey Psychiatric Institute, P.O. Box 1000, Princeton, New Jersey.

Membership in both Societies is limited to those who are actively engaged in ballistocardiographic research.

The Secretary General of The World Medical Association has requested that medical associations and doctors of the world provide MEDICAL SUPPLIES AND FUNDS FOR THE RELIEF OF THE EARTHQUAKE VICTIMS IN CHILE.

Assistance should be addressed to: Dr. Rolando Castanon, Colegio Medico de Chile, Miraflores No. 464, Santiago, Chile.

THE PAKISTAN MEDICAL ASSOCIATION cordially invites representatives from the Medical Associations of the world to attend the VI Pakistan Medical Conference, Karachi, Pakistan, Nov. 25-28, 1960.

Additional information with respect to this conference may be obtained from: Dr. H. R. Khan, Secretary General, Pakistan Medical Association, Garden Road, Karachi, Pakistan.

THE FIRST INTERNATIONAL CONGRESS OF HISTOCHEMISTRY AND CYTOCHEMISTRY will be held in Paris, France, from Aug. 28 to Sept. 3, 1960. It is organized under the auspices of the Société Française d'Histochimie in collaboration with the histochemical societies in existence all over the world, especially the American Histochemical Society, the Deutsche Arbeitsgemeinschaft für Histochemie, the Société Belge d'Histochimie, the Italian and Japanese histochemical societies, and several nonautonomous sections of histochemistry.

All correspondence on scientific matters pertaining to the Congress should be addressed to: Dr. R. Wegmann, Institut d'Histochimie Médicale, 45, rue des Saints-Pères, Paris (6e), France. The full program will be sent upon request.

For several years, scientists interested in basic problems of congenital malformations have held informal conferences in which questions of common interest were discussed. Anatomists, biochemists, embryologists, geneticists, obstetricians, pathologists, pediatricians, plastic surgeons, and others attended these conferences which were supported in part by the Association for the Aid of Crippled Children, New York, N.Y., and the Human Embryology and Development Study Section of the National Institutes of Health. With the increased interest in recent years in this area, it was felt that there was a need for a Society to hold regular meetings in which investigations concerned with the etiology and morphogenesis of congenital malformations could be presented and discussed. Following the Fourth Tetralogy Conference, which was held at the Memorial Sloan-Kettering Cancer Center in New York City and was attended by 76 scientists from Canada, England, France, Germany, and the U.S.A., THE TETRALOGY SOCIETY was formed for the purposes outlined above.

Inquiries about THE TETRALOGY SOCIETY should be directed to: Dr. Marjorie M. Nelson. Department of Anatomy, University of California School of Medicine, San Francisco 22, Calif,